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ATYPICAL FORM OF PAGET'S DISEASE APPEARING AS GENERALIZED OSTEOSCLEROSIS

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In the domain of bone disease, unlimited information is yet to be gleaned by continued painstaking pathologic investigation. Intensive study would undoubtedly be of prodigious value in the clarification and interpretation of many puzzling features of Paget's disease. Only recent work has revealed that the hitherto accepted concept of this disease is neither complete nor comprehensive. The prevailing premises that the condition is rare, that the tibia is the bone most frequently involved and that the calvarium is generally thickened no longer hold in the light of these studies. Neither does the view wholly obtain that the changes in the bones are necessarily associated with softening, thickening and deformity, producing a clinical picture such as was originally drawn by Paget.[1] Through Schmorl's observations it became evident that the vertebrae (particularly the lumbar) and the sacrum are most susceptible to involvement by this disease. Frequently, the lesion is limited to only one or more of the lumbar vertebrae or merely to a portion of the sacrum. In such instances, there need be no clinical manifestation of the condition, and roentgenographically the implication may not even be discernible. Furthermore, by systematic postmortem examination of bones, he found that about 3 per cent of those in persons past 40 years of age were affected by some degree of Paget involvement.[2]

In a review [3] written a short while ago, a rather extensive survey was made of Paget's disease. Special emphasis was laid on the histologic criteria for diagnosis (the mosaic architecture), the evolutionary progress of the changes in both cortical and spongy bone and the activity of the periosteum in initiating thickening of tubular bones (as demonstrated by a case independently observed). Freund [4] was the first who was able to demonstrate conclusively that periosteal proliferation sometimes reaches such proportions as to be easily discernible with the naked eye. In my case it was evident that gross subperiosteal new

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1. Paget, J.: Tr. Roy. M. & Chir. Soc., London **60**:37, 1877.
2. Schmorl, G.: Virchows Arch. f. path. Anat. **283**:694, 1932.
3. Jaffe, H. L.: Arch. Path. **15**:83, 1933.
4. Freund, E.: Virchows Arch. f. path. Anat. **274**:1, 1929.

bone formation was only an exaggeration of the process that ordinarily leads to thickening of the bone in Paget's disease and that generally can be seen only under the microscope.

The horizon embracing Paget's disease is constantly widening. Pines [5] (working under Erdheim) has even more recently described a porotic calvarium which was not thickened and which, in the gross, suggested Recklinghausen's disease rather than Paget's disease. Microscopically, in addition to its porotic areas, certain sclerosed regions presented primitive bone centrally and lamellar bone peripherally, with the Paget mosaic architecture in the lamellar bone. This case, which was considered an unusual porotic form of Paget's disease (confined to the cranial bones), seems to throw some light on those poorly understood lesions of the calvarium which are so difficult of interpretation and which have heretofore been described, especially roentgenographically and clinically, under divers titles. Pines' pathologic study may be of great value in clarifying the understanding of the calvarial lesions described as circumscribed osteodystrophy.[6] Furthermore, it is definitely helpful in interpreting the significance of the circumscribed porotic lesions which occasionally appear in the calvarial bones (with or without Paget-like involvement in other portions of the calvarium or of other bones).[7]

The study of a case which further supports the possibilities of variation in the pathologic manifestations of Paget's disease is here recorded. The calvarium, spine, innominate bones, sternum and ribs removed from a patient who died of uremia showed an advanced osteosclerosis which was intense in certain areas. The calvarium was heavy and sclerotic, but was not noticeably thickened. Paget's disease was nowhere plainly suggested in the gross, except possibly in the ilia. Microscopically, the osteosclerosis, except in the more intense areas, was not associated with scarring of the marrow (the marrow remained myeloid and fatty); the trabecular thickening was everywhere the result of slow new bone deposition following slowly progressing resorption. Such thickened trabeculae were constituted of lamellar bone and showed an increased number of cement lines. The cement lines, on the whole thin and somewhat irregular, separated numerous fragments of lamellar bone. The Paget nature of the osteosclerosis was strongly suggested by this histologic appearance. It was confirmed to a greater degree by the microscopic features in the areas of more intense sclerosis where complete trabecular reconstruction had occurred, where the picture in

5. Pines, B.: Virchows Arch. f. path. Anat. **287**:714, 1933.

6. Frangenheim, P.: Verhandl. d. deutsch. path. Gesellsch. **21**:49, 1926.

7. Sosman, M. C.: Radiology **9**:396, 1927. Schueller, A.: Med. Klin. **25**: 631, 1929. Weiss, K.: Fortschr. a. d. Geb. d. Röntgenstrahlen **41**:8, 1930; **42**: 376, 1930. Meyer-Borstel, H.: ibid. **42**:589, 1930. Kasabach, H. H., and Dyke, C. G.: Am. J. Roentgenol. **28**:192, 1932.

regard to the mosaic reached a somewhat more characteristic appearance and where the myeloid and fatty marrow had been converted into fiber marrow. But even in such areas, the gross appearance was not that of typical Paget's disease. Thus, in this case, the gross pathologic changes of Paget's disease were manifested essentially by an osteosclerosis. There can be no doubt that in the diagnosis of Paget's disease, histologic appearances take precedence over clinical features and even over gross aspects.

Several references have until now been made to the mosaic architecture of typical Paget bone. The newly formed lamellar bone in Paget's disease has this distinctive appearance, and to Schmorl must be credited the bringing into relief of the value of this rather specialized histologic feature for diagnosis. Completely and typically developed new Paget bone is found, on microscopic examination, to consist of irregular segments of lamellar bone (*breccie*), which are separated by short, irregular and often somewhat toothed cement lines. Furthermore, in Paget lamellar bone that is being rapidly built up, the cement lines may be short and stain deeply. Thus, an area of bone totally transformed and completely involved by typical Paget's disease consists, microscopically, of tiny fragments of lamellar bone fitted into one another like an irregular mosaic, with little tendency for the bone fragments (as pointed out by Freund) to be arranged about vessel canals to form haversian systems. The more rapid and florid the progress of Paget's disease, the more characteristically does the mosaic appearance develop; healing of Paget's disease is associated with a tendency for the mosaic arrangement to disappear. The slow progress of the development of the osteosclerosis in the case here reported was the factor to some degree modifying the typical mosaic arrangement.

REPORT OF A CASE

The patient, aged 58, a house painter, gave a history of one lead colic attack at the age of 38 and typhoid fever at 28; he had had swelling of the ankles and dyspnea on exertion, with an attack of cardiac pain four years before; he entered the hospital specifically for inability to void urine without catheterization. Examination disclosed prostatic enlargement, cardiac hypertrophy and chronic nephritis. There was 2 plus albumin in the urine, with fixation of the specific gravity at about 1.010; on admission blood analysis showed 60 per cent hemoglobin, 3,840,000 red cells and 11,300 white cells (the differential count showed nothing unusual); there was no basophilic stippling; the blood urea was 42 mg. per hundred cubic centimeters, and it rose to 80 mg. before death; the blood pressure was 134 systolic and 90 diastolic.

Two days after a transurethral resection of the prostate under spinal anesthesia, the patient became seriously ill, with elevation of temperature and evidences of meningeal irritation. Lumbar puncture showed a turbid spinal fluid with a cell count of about 2,000, normal sugar and sterile culture; the spinal cell count finally diminished to about 100 cells. He was treated by spinal drainage, and on culture

several of numerous specimens showed pleomorphic, hemolytic streptococci, which grew slowly. Though the meningeal irritation receded, evidences of increasing uremia appeared, and finally pulmonary edema developed and the patient died.

Pathologic Changes.—Other than the changes referable to the bones, the gross and microscopic examinations disclosed contracted kidneys on an arteriovascular basis, arteriosclerosis of the aorta and coronary arteries, terminal acute pericarditis, cardiac hypertrophy and dilatation, bilateral hydrothorax, beginning bronchopneumonia and low grade meningitis (there was a scattering of leukocytes over the pia-arachnoid with very little fibrin).

Vertebral Column: Gross appearance. The vertebral column was removed from the fourth dorsal vertebra down through and including the sacrum and coccyx.

A slight degree of upper dorsal kyphosis existed, and there was some diminution in flexibility of the upper dorsal spine. The individual vertebrae appeared to be of good size. While normal values for measurement are not readily obtainable and comparisons are unsatisfactory because of considerable individual variations, nevertheless, the lumbar vertebrae gave the impression that they were slightly larger than normal in the anteroposterior diameters. The upper and lower surfaces of the dorsal vertebrae were on the whole quite straight; these surfaces of the lumbar vertebrae were slightly depressed in conformity with the slight expansions of their disks.

On sagittal section, the disks between the lumbar vertebrae were found slightly expanded, while the others were of about average thickness. Throughout, the intervertebral disks were brown (fatty degeneration being clearly discernible in the gross); the brown degeneration of the lumbar intervertebral disks was most prominent. The turgor of the nuclei of the disks was for the most part well maintained; there were small prolapses of the intervertebral disks from the upper surface of the tenth, eleventh and twelfth dorsal disks (fig. 1). A small prolapse from the lower surface of the second lumbar disk was apparent. There was considerable tendency to calcification of the anterior portions of the annuli fibrosi of the dorsal disks. The disk between the fifth lumbar and the sacral promontory was partially calcified; the first sacral disk (as well as the lower two) was still present although calcified; the second and third sacral disks had almost completely vanished; the coccygeal disks were present. Lipping of the upper and lower margins of the vertebral bodies was clearly observed in the macerated portion of the spine; this was the result of osteophytic overgrowth below the anterior ligaments. Laterally, between the seventh and eighth dorsal vertebrae, two large apposed and overlapping osteophytes were seen.

The appearance of the spongiosa of the vertebrae and sacrum was the noteworthy feature in the sagittal section of the spine. The trabeculae everywhere were thickened, and the spongy structure was quite compact (fig. 1). The thickening of the trabeculae had resulted in a reduction in size and a change in the direction of the marrow spaces; this applied to the bodies and processes alike. (The spongiosa of a normal vertebral body is delineated by major vertical lines and minor horizontal lines forming a honeycombed structure with fairly regular marrow spaces.) In these vertebral bodies the direction of the trabecular lines was completely distorted; the marrow spaces were marked by irregularity of shape and size, and were greatly reduced (many were so small as to be discernible only in the macerated specimen).

Moreover, certain vertebrae had dense sclerotic patches which were strikingly prominent in the wet preparation. One such area was located in the posterior half of the body of the first lumbar vertebra extending from disk to disk (fig. 1). In

Fig. 1.—A wet specimen from the spine, including the tenth, eleventh and twelfth dorsal and the first lumbar vertebrae and their intervertebral disks. The tenth, eleventh and twelfth dorsal disks show small prolapses through their upper surfaces. The spongy trabeculae of the vertebral bodies are evidently thickened, and the marrow spaces present marked irregularity in size and shape. A patch of dense sclerosis is observed in the posterior half of the first lumbar vertebra and in the spinous process of this vertebra; the dense sclerosis in the body and spinous process of the eleventh dorsal vertebra is also clearly evident.

the wet preparation, these intensely sclerotic regions were characterized by a whitish-yellow coloration, a smooth cut surface and a dense consistency when scraped with the nail. Under a hand magnifying glass, such an area in a macerated preparation displayed the features of the adjoining less sclerosed spongiosa to a markedly intensified degree by virtue of its greater compactness

Fig. 2.—Macerated preparation from the other half; it includes the tenth, eleventh and twelfth dorsal and the first and second lumbar vertebrae. All of the vertebrae show osteosclerosis with the more intensified sclerosis in the eleventh dorsal and the first lumbar vertebrae.

(fig. 2). The spinous process of this body similarly showed dense sclerosis. An area of equally intensified sclerosis was observed in the posterior portion of the body of the eleventh dorsal vertebra, while the entire body of the fourth dorsal vertebra was so converted.

Thus, the vertebrae manifested generalized osteosclerosis of the bodies and processes, which was intensified in certain of the bodies, particularly in the first lumbar, the eleventh dorsal and the fourth dorsal; in these vertebrae, the intense sclerosis extended into the processes.

On sagittal section of the sacrum, sclerosis was again apparent, being quite intense in its upper two-thirds, most of which was very compact. This process was more or less uniform, extending from the anterior to the posterior surfaces.[8]

Microscopic appearance. Sections for histologic study were taken from a number of different vertebral bodies and from the sacrum and coccyx. In regard to the major pathologic changes, the descriptions will be confined (1) to the appearance of the tenth dorsal vertebra, which showed the generalized but less intense osteosclerosis, (2) to the first lumbar vertebra, which in addition had a large patch of more intense sclerosis posteriorly, and (3) to the upper portion of the sacrum, which evidenced a more or less generally intense sclerosis.

1. The tenth dorsal vertebra presented a general trabecular thickening even under the lowest magnifications (fig. 3*A*). In such a survey it could be seen that the thickened trabeculae were composed throughout of lamellar bone, while the narrowed intertrabecular marrow spaces contained myeloid and fatty marrow which was not apparently abnormal. Immediately beneath the intervertebral disks, the spongiosa was, on the whole, most compact. Two small intervertebral disk extensions, one from the upper and the other from the lower disk, were observed, but the protrusions were limited to small zones immediately beneath the defective annuli. There was no framing or compacting of the sclerotic trabeculae at the anterior or posterior margins of this body.

Higher magnification disclosed microscopic abnormality of all the thickened trabeculae (fig. 3*B*). This deviation from the normal was evidently the result of gradual resorption occurring on the surfaces of many of the trabeculae, followed by new bone deposition. Many of the trabeculae, showing resorption on the surfaces, contained osteoclasts in sparse numbers in Howship's lacunae; where resorp-

8. Comparison of the sagittal section of this spine with that of a spine involved by typical Paget's disease would show striking contrasts. In the latter type of involvement, it is to be observed that the vertebral bodies show thickened, closely set trabeculae framing the body peripherally. Furthermore (in contradistinction to the appearances observed in the vertebral bodies of the case reported), the more centrally placed trabeculae are much fewer in the more typical involvement. They usually are distinct as pillars with irregular surfaces. The differences in appearance between the typically involved spine and the spine under observation are also clearly marked on roentgenographic examination. In the usual type of involvement, the roentgenogram of a spine extirpated from the body will show the peripheral condensation of trabeculae and the central rarefaction, which, of course, this spine did not evidence. It did show a diffuse sclerosis, and it is worthy of mention that an antemortem roentgenogram did not suggest the presence of Paget's disease, although it could be recognized in the plates that a sclerosis existed. It is especially noteworthy that in this spine, although the involvement was diffuse, no serious deformations in the shape of the vertebral bodies had occurred. This often takes place in the bodies of spines with the more typical Paget's disease; in such the more common deformity is a reduction in the superior-inferior diameter of the body and an increase in the anteroposterior diameter (the latter being due to periosteal growth). While there was no reduction of the superior-inferior diameter in this case, the lumbar vertebrae presented a possibly slight increase in their anteroposterior diameters.

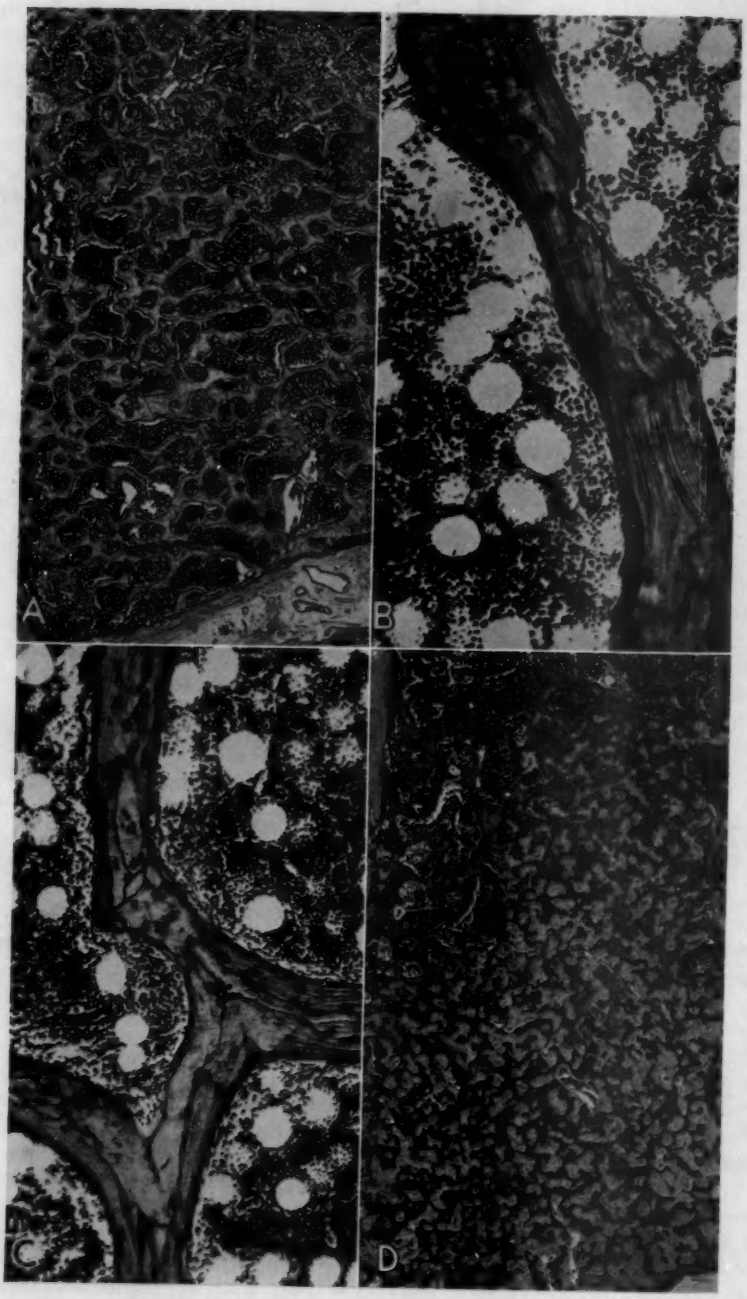

Figure 3

Fig. 3.—*A* shows a very low power survey of the anterior half of the body of the tenth dorsal vertebra. The general trabecular thickening is apparent, and the narrowed intertrabecular marrow spaces contain myeloid and fatty marrow; × 5. *B* gives the architectural detail of one of the many trabeculae seen in *A*. The lamellar construction of the bone is illustrated. On the right above the middle, a Howship lacuna with osteoclasts is seen. Slightly below this, flattened osteoblasts are observed depositing new bone. Farther below, a fragment of newly formed bone, delimited by a cement line, appears on the surface of the trabecula. It is plain that there is no scarring or fibrosis of the myeloid marrow. The cement lines are irregularly directed; × 200. In *C*, the trabeculae show still more changes in the minute architecture. Their composition of irregular fragments of bone, separated by thin cement lines, many of which are short, can plainly be seen. On the left, new deposition of bone is evident; resorption is in progress. To the right, some of the bone shows poor staining of the ground substance and few bone cells; × 135. *D* is a low power survey of the posterior half of the first lumbar vertebra. It shows the dense area of sclerosis with a zone of thickened trabeculae still containing myeloid marrow above. The reconstruction of the trabecular architecture and the loosely cellular fiber marrow of the densely sclerotic patch are visible; × 5.

tion defects were being filled out by new bone, such bone seemed to be deposited by flattened spindle-like osteoblasts; in other words, it was not a deposit of connective tissue new bone from the marrow. Often, one of the trabecular surfaces manifested resorption while the opposite surface was still smooth and regular, or this surface had a narrow zone of newly deposited bone. Furthermore, evidence of mild resorption and new bone formation was also to be observed on the walls of some of the haversian canals in thickened trabeculae. The histologic examination up to this point disclosed trabecular thickening to be the result of lamellar new bone deposition apparently following in the wake of initial resorption; it is necessary to acknowledge that the new deposition in order to cause trabecular thickening must be excessive or more than compensate for the resorption.

The other feature clearly evident is that there was no scarring or fibrosis of the myeloid marrow, although throughout the section none of the bony trabeculae appeared normal (fig. 3 *A* and *B*). When the depressions on the trabeculae that had resulted from resorption were examined, a few spindle cells were seen lining them. Close examination of the myeloid marrow in such a vicinity demonstrated that the small number of spindle connective tissue elements that appeared in conjunction with the resorptive process were derived from the endosteum. This endosteum normally sheathes and separates the myeloid marrow from the trabeculae. This fact is worthy of emphasis as it strikingly demonstrates that the changes of Paget's disease are not initiated primarily in the myeloid marrow, a point which Schmorl [2] emphasized.

On still closer microscopic inspection, one could not fail to notice that the minute architecture of these thickened trabeculae was everywhere abnormal (figs. 3 *B* and *C*). On the whole, whether considerably thickened or not, they were seen to be composed of numerous irregular fragments of lamellar bone, separated by relatively thin and short cement lines; these lines were much more numerous, more irregular and darker staining than the cement lines of normal spongy bone. (These thickened trabeculae were histologically different in appearance from the thickened trabeculae of the osteosclerosis that may be associated with myelogenous leukemia; in the latter, thickened trabeculae do not show such irregularities of cement lines, nor are they constructed of so many fragments of lamellar bone. From the foregoing facts the microscopic construction of the spongy trabeculae in this case forcibly suggested the mosaic architecture of Paget's disease, although nowhere in the section did it completely duplicate the appearance of the typical mosaic formations observed in florid Paget's disease.

It was also plainly discernible in the section that considerable bone within the substance of the thickest trabeculae had a peculiar appearance. In such areas, the bone cell lacunae were round or tended to be so; in places, this reached a striking degree. When it did so, it was apparently allied with distortion and disintegration of the canaliculi and bone cell processes, and with darker staining and granulation of the ground substance. There was likewise a loss of the lamellar arrangement in those areas showing the process in its most advanced stages. The fragments of bone most likely to present this appearance were those lying deepest within the substance of the thick trabeculae, although it could be seen on the surfaces of trabeculae, especially close to areas in the process of resorption. I have gained the impression that this is a regressive change, unrelated to the question concerning the blue-staining, primitive bone inclusions which are to be observed in the mosaic bone in florid cases of Paget's disease.[9]

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9. The osteophytic overgrowths and the periphery of the vertebral bodies were composed of trabeculae of lamellar bone with fatty marrow between them. The trabeculae were thick and consisted of a large number of fragments.

2. In the gross (figs. 1 and 2), the first lumbar vertebra presented a patch of dense sclerosis in addition to sclerosis of the rest of its substance; on microscopic examination, several notable differences distinguished this zone of dense sclerosis from the tenth dorsal vertebra. Its dense sclerotic area retained no semblance of the original trabecular arrangement. Furthermore, the myeloid marrow had been practically completely replaced in this area by loosely cellular fiber marrow (fig. 3*D*). Higher power examination (fig. 4*A*) of this dense sclerotic area showed the absence of regular, normal formations of trabeculae. The original trabeculae had been completely replaced, and newly formed calcified bone was substituted for it. The bone here was everywhere in an active stage of reconstruction. On the whole, new deposition was rather excessive and the new bone, well calcified, was deposited in bizarre, grotesque or coral-like arrangements. The resorption was rather extensively established, particularly in the peripheral portions of the patch; where resorption was in progress, there were Howship's lacunae and osteoclasts. The new bone formation was through the medium of flattened osteoblasts; one of the striking elements in this regard was the very slight number of osteoid margins. When these were present, the overlying osteoblasts were taller. It was clearly evident that the newly deposited calcified bone was also rapidly resubjected to resorption, partly or wholly.

One of the notable features of this newly formed bone was that many of its component fragments showed numerous large and grouped nuclei, more reminiscent of the nuclear appearances of fiber than of lamellar bone. It appeared as a puzzling feature that baffled analysis. Although this bone suggested reticular fiber bone, it was not in any way connected by fibers with the fiber marrow, and it seemed definitely to be deposited by flattened osteoblasts. While lamellar construction of the ground substance was noticeable in places, in other places it was impossible to perceive such an arrangement. In the deposition of new bone, numerous small haversian canals were produced. One is therefore led to conclude that the newly formed bone in these sclerotic areas was quite calcified, deposited by osteoblasts, showing definite lamellar arrangement in parts; the portions not showing the lamellar arrangements were nevertheless more evolved bone. The cement lines were fairly numerous; some were thick; all were on the whole short; they were not so irregular, dark staining or numerous as those in typically formed Paget bone. This fact makes it evident that the bone resorption and deposition in this densely sclerotic area did not proceed at the rapid pace that it does in typical Paget's disease. Furthermore, the slowing of the process of new bone formation permitted calcification of the new bone which was reflected in the hardness and rigidity of the bones in this case.

The fiber marrow was composed of loose spindle connective tissue the cells of which were apparently connected by reticular processes. It contained a scattering of cells which included lymphocytes, plasma cells and mononuclear phagocytes. Within this fiber marrow, a few islands of myeloid and fatty marrow were still discernible; these islands were immediately surrounded by a layer of phagocytic cells of various thicknesses; the retained islands of myeloid marrow were being walled off and apparently crowded out in the course of the disease. Replacement of the myeloid marrow by fiber marrow was not the result of initial changes in the myeloid marrow. The fiber marrow was quite vascular in places, particularly so in the zones bordering the islands of retained myeloid marrow; occasional small amounts of fresh hemorrhage could be seen here. However, the fiber marrow contained neither the large quantities of blood pigment nor the numerous engorged vessels so common in the fiber marrow of Paget bone.

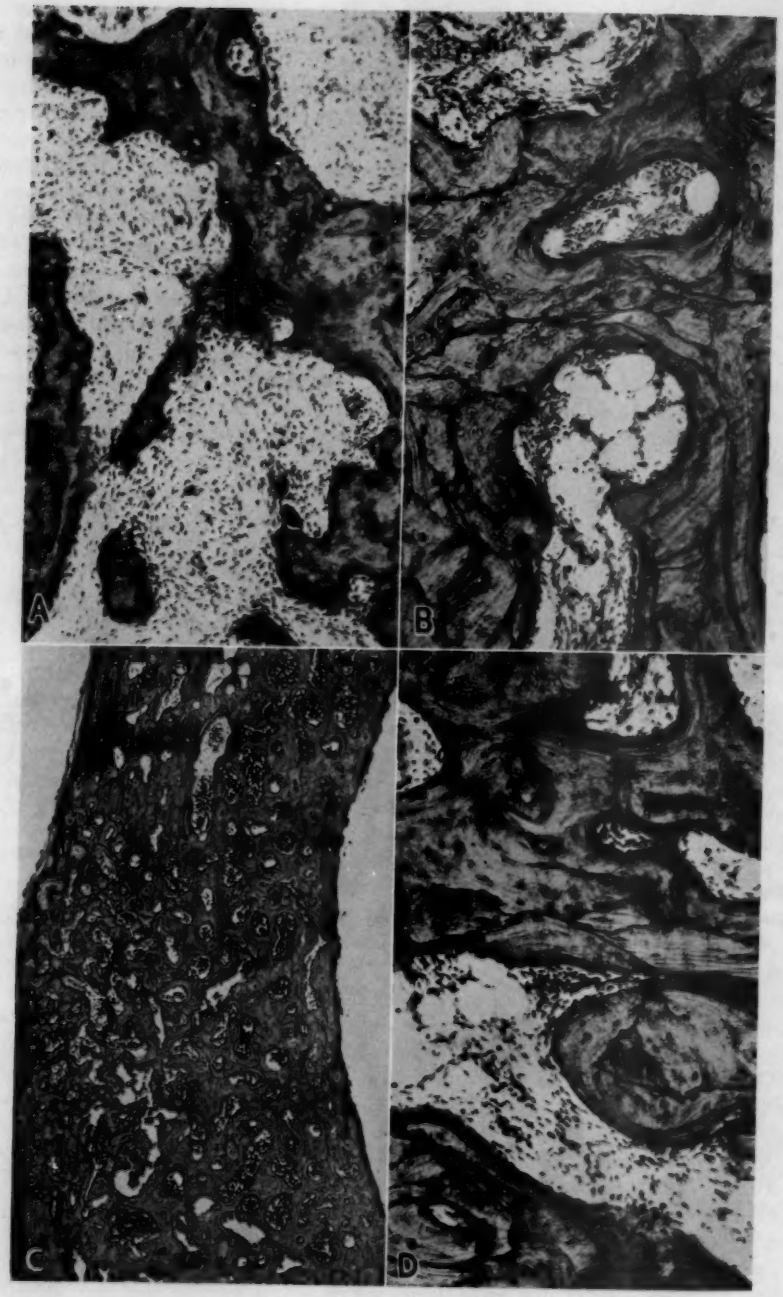

Figure 4

Fig. 4.—*A* shows the bone and fiber marrow, typical of the densely sclerotic area in the first lumbar vertebra. The new bone is calcified, and flattened osteoblasts are observed on many of the new trabecular surfaces; osteoid margins are not prominent. Resorption is also apparent. The new bone depositions are of irregular shape. The lamellar nature of this new bone is not very clear, except in an occasional area. The cement lines are on the whole short and irregular; some are thick. The fiber marrow is composed of loose, spindle, connective tissue; × 135. *B* shows thickened trabeculae in the sacrum. They are composed of numerous fragments of bone, separated by thin and somewhat irregular cement lines. Most of this bone is clearly lamellar. The surface of some of the trabeculae show the deposition of new bone; × 135. In *C* is the parietal bone, showing diffuse osteosclerosis, with the focus of transformed calvarial bones in the left middle region. The marrow here is fibrous and the enlarged spaces are open to beneath the pericranium; × 5. *D* shows thick trabeculae within the transformed area illustrated in *C*. These are composed of fragments of newly formed bone; most of them are definitely lamellar. The cement lines are numerous fairly thick and somewhat irregular; × 135.

Thus, the densely sclerotic area showed, as described, fiber marrow and completely transformed bone; the more simply sclerotic area adjacent to it revealed myeloid and fatty marrow with thickend trabeculae of definite lamellar construction. In the transition zone, some trabeculae had myeloid marrow on one surface, which was rather smooth, and fiber marrow on its opposite surface, which was markedly irregular. These transition trabeculae indicated the essential cause of differences between the densely sclerotic and the simply sclerotic bone. It is to be related to more rapid resorption associated with more excessive deposition of bone. The trabeculae, surrounded by myeloid marrow, near the densely sclerotic area, showed quite active resorption and deposition on their surfaces, but their reconstruction was not complete. The trabeculae farthest from the densely sclerotic area demonstrated considerable new deposition of lamellar bone and a marked increase of the cement lines (fig. 3*C*), but these were not as irregular as those in the trabeculae adjacent to the densely sclerosed area.

3. Microscopic examination of the proximal sacral segment, which in the gross was densely sclerotic almost entirely, revealed practically all of the histologic features so far described in the tenth dorsal and first lumbar vertebrae. Most of the sclerotic area containing fiber marrow extended from the middle of the upper intervertebral disk into the substance of the segment. A very small patch with fiber marrow was also located posteriorly and inferiorly in this sacral segment. Most of the inferior, a good portion of the superior, the anterior and the posterior borders of this sacral segment were constituted of extraordinarily thickened trabeculae between which lay myeloid and fatty marrow. These extremely thickened trabeculae (fig. 4*B*) above the middle of the lower disk were composed of lamellar bone; they were divided into numerous fragments by thin and somewhat irregularly directed cement lines. The lacunae of the cells within many of the component fragments were large and round. However, most of this bone was quite clearly lamellar bone. The surfaces of some of these trabeculae showed evidences of active resorption with osteoclasts in Howship's lacunae, as well as lamellar new bone deposition. The major marrow between these thickened trabeculae was myeloid and fatty. The more sclerosed area containing fiber marrow was like the analogous area in the first lumbar vertebra—in a stage of much more active transformation. The completely transformed trabeculae showed the tendency to mosaic architecture. No extensive primitive reticular bone formation was seen in the osteoblastic fiber marrow.

Sternum and Ribs: The sternum was involved by generalized simple sclerosis. On sagittal section its surface showed the same type of lesion as that described for the ninth dorsal vertebra (fig. 5). The closely set trabeculae extended from the inner to the outer cortical surface. This type of involvement was, of course, strikingly different from the appearance of the sternum involved by the more typical polyostotic Paget's disease, in which thick, condensed and pumice-like trabeculae frame the margins of the body and manubrium. A number of ribs were also studied. Outwardly, they had no appearance of abnormality. When sectioned sagittally, however, the marrow spaces were narrowed; although the cortices were not unusually thickened, they were quite compact; the trabeculae were thickened. On microscopic study, these thickened trabeculae were surrounded by normal-appearing myeloid and fatty marrow; they showed narrow margins of newly deposited bone in various places and, simultaneously, slight but definite evidences of active resorption. The thin cement lines were numerous and quite irregular in direction. An occasional vessel canal of the cortex contained fiber marrow, while subperiosteally there were slight resorption and new bone formation. In none of the sections examined was there evidence of scarring of the

myeloid marrow. The costal cartilages were calcified and in places manifested central ossification and subperichondrial ossification. The bone trabeculae within the substance of the costal cartilages and underneath the perichondrium were fairly thick and demonstrated an abundance of cement lines.

Calvarium: Gross appearance. The part taken for study composed the greater part of the frontal and occipital bones, both parietals, portions of the squamae of the temporals and parts of the great wings of the sphenoids. Its outer surface was fairly smooth; its shape, when viewed from above, was more or less oval, and the conformation was regular. All of its component bones were firmly synostosed. On the outer surface, remains of the coronal suture, extremely serrated, and the remains of a markedly serrated sagittal suture were still to be seen. The sphenofrontal and squamosal sutures were completely obliterated. The condition of the lambdoidal suture cannot be recorded as that section of the calvarium was not retained after parts had been taken for histologic study.

The inner surface of the skull cap did not present prominent depressions or furrows (fig. 6*A*); the depression for the convolutions of the cerebrum and the

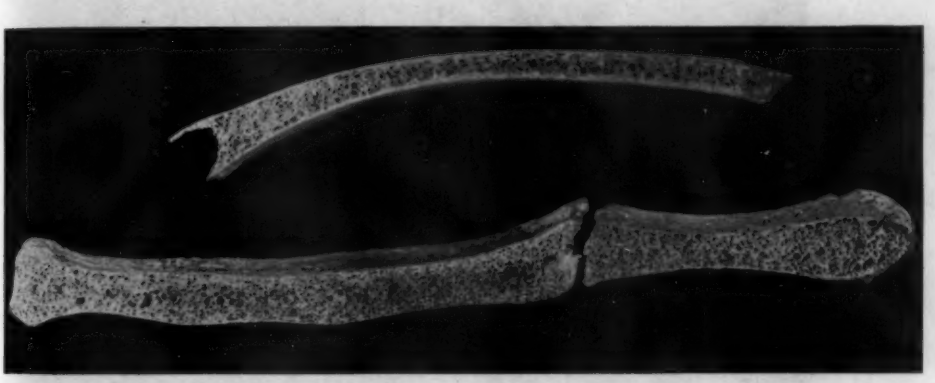

Fig. 5.—A rib and the manubrium and body of the sternum, in sagittal section. The diffuse osteosclerosis, owing to densely set, thick trabeculae, is obvious.

furrows for the lodgment of branches of the meningeal vessels were not as deep as might have been expected. Nor was there present, except in the very front of the calvarium, a longitudinal groove for the lodgment of the superior sagittal sinus. Furthermore, no prominent depressions for the arachnoid granulations were to be observed. Only the faintest traces of the coronal and sagittal sutures were seen on the inner calvarial surface.

Two centimeters behind the coronal suture, in the midline (fig. 6*A*), the calvarium revealed a thickness of 6 mm.; at other points from the midline of the frontal section, the thickness was as much as 8 mm. At 6 cm. behind the coronal suture in the midline, the thickness through the central portions of the parietal bone measured 9 mm. The squamae of the temporal bones measured between 3.5 and 6 mm. in thickness. The frontal bone, slightly anterior to the frontal eminences, measured between 3.5 and 5 mm. No portion of the calvarium exceeded 9 mm., although in many places it was thinner.

Gross examination exhibited a diploic structure everywhere, tending toward obliteration (fig. 6*A*); in places it had practically disappeared. Where it had, the bone was extremely compact; on the whole, these regions were thinner than those

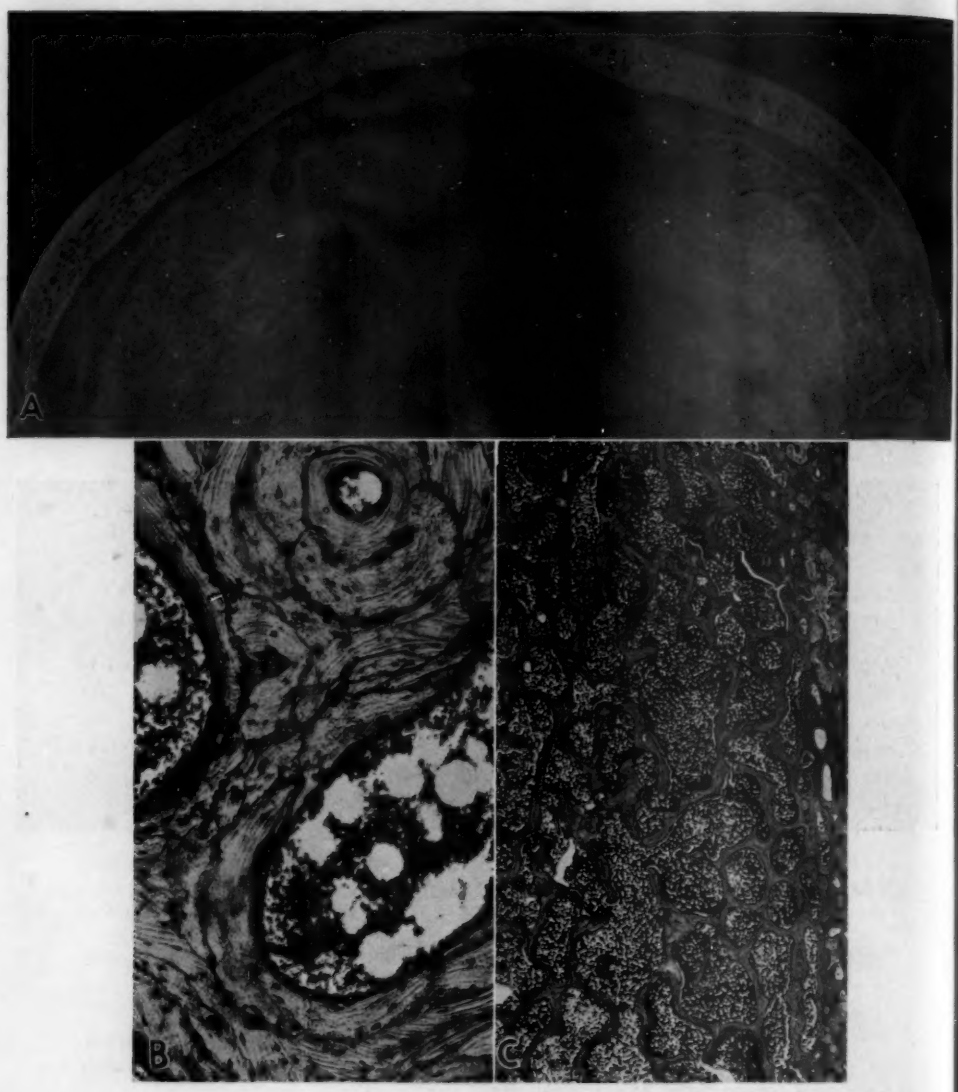

Fig. 6.—*A*, frontal section through the calvarium, 2 cm. behind the coronal suture in the midline. The tendency to obliteration of the diploe can be seen. The inner surface of the skull cap does not present any prominent depressions or furrows. On the whole, the outer table is thicker than the inner table. *B*, thickened trabeculae with diploic spaces, containing myeloid and fatty marrow. These trabeculae are from the nontransformed portion of the parietal bone. These thickened trabeculae plainly evidence the deposition of new bone which is present in the form of small fragments (breccie) separated by thin cement lines; × 135. *C*, a portion of the ilium through the anterior half. It shows a cortical layer on the right, composed of compact lamellar bone with haversian systems. The marrow between the thickened trabeculae is myeloid and fatty; × 5.

retaining diploic structure. Such obliteration was observed in portions of the frontal bone and even in the parietal bone close to the sagittal structure. Where the diploe were present, it was seen that the spaces were markedly reduced in size, and that the trabeculae were extraordinarily thick and closely set. With regard to the outer and inner tables, it is rather difficult to state precisely details concerning their gross features; in the compact areas no distinct tables could be observed; in the more diploic areas distinct table development was seen. Where distinctions between the tables were clearly manifest, the outer table seemed generally thicker than the inner table (fig. 6*A*). It was evident on gross examination that the portion of the calvarium studied was noticeably heavier than ordinarily; its increase in weight was quite apparently attributable to increased compactness rather than to any appreciable increase in thickness.

Microscopic appearance. A number of sections from various parts of the calvarium were examined histologically; all plainly demonstrated, as had been suggested by the gross appearance, that there was a condensing or osteosclerotic process in progress; it was akin to the sclerosing process observed in the other bones.

A section, which included a portion of the parietal and a fragment of the squama of the temporal bone, showed a distinct middle diploic zone composed of large and small spaces separated by thick bony walls. The diploic zone encroached on the inner table, but the outer table was quite prominent and thick. The surface of the outer table was covered by a thick layer of ground lamellae between which were thick appositional cement lines (*Ansatzlinie* of von Kölliker); very superficially, these appositional cement lines were so numerous as to give the section in this region a blue appearance. The outer surface of the outer table therefore showed evidence of slow and halting new bone deposition; in this section, there was practically no indication of resorption on the outer surface of the table. The outer ground lamellae, with their interposed, appositional cement lines, extended deeply into the substance of the outer table, but were disrupted by a fairly considerable number of thick-walled haversian systems with thick peripheral cement lines. These haversian systems were composed of lamellar bone with nuclei that stained well, but from the appearance of their cement lines they gave indubitable evidence of active reconstruction. The deeper portion of this table was composed of disrupted fragments of ground lamellae situated between haversian systems; added to these were some disrupted fragments of haversian systems. Much of this interstitial bone showed poor staining of the nuclei or complete absence of nuclear staining; portions also showed poor staining of the ground substance. Apparently, therefore, much of this bone was dead or dying. A number of the haversian canals of the outer table were filled with fiber marrow and, as stated, definite evidences of active resorption were visible on their walls.

Some of the diploic spaces contained fatty marrow; most of them still contained myeloid and fatty marrow. Their trabeculae were quite thick; some contained haversian spaces. The thickening of the trabecular walls (as elsewhere in the bones) can definitely be ascribed to the result of active new bone deposition on their surfaces following resorption. Practically everywhere on the surface of the trabeculae, resorption and deposition were in progress. The process seemed to be fairly active, though slow, without participation of the myeloid marrow. The thickened trabecular walls were built up of numerous small fragments of lamellar bone, irregularly arranged. The numerous interposing cement lines were on the whole thin, only a few being somewhat thickened but not abnormally. The nuclei of the more deeply placed lamellar bone of these trabeculae were likely to stain poorly.

The inner table was not unusually prominent, being reduced for the most part at the expense of the diploe. It contained only a few haversian systems. The innermost surface of the inner table was lined by inner ground lamellae with a few appositional cement lines. The number of inner ground lamellae was noticeably less than on the outer surface of this section. Other sections from the parietal bone essentially duplicated the appearances described.

However, one of the sections presented a rather distinctive aspect; this section, from the parietal bone farther posteriorly, included the obliterating sagittal suture and a portion of the other parietal bone. Its greatest thickness was about 9 mm. It retained a diploic structure, but the diploe were narrow, and the trabeculae were thick. Microscopic study revealed a portion of the bone included in this section as strikingly different from the rest of the section and from any of the appearances so far described in the calvarium (fig. 4 *C*). Here, the section showed that the bone had undergone an extensive architectural transformation. It appeared quite evident that within this area there had been extensive resorption with new bone formation and reconstruction on the walls of the diploic and haversian spaces. Haversian spaces opened beneath the pericranium; these spaces were filled with fiber marrow and were lined by new bone with large nuclei. The thick trabeculae within this focus were observed to be composed of fragments of newly formed bone, most of them definitely lamellar in structure, although some showed very large nuclei. The cement lines between these fragments were fairly thick and somewhat irregular (fig. 4 *D*). At the periphery of this portion of active transformation, evidences of resorption with osteoclasts were seen.

The active transformation had extended from the outer surface to about the middle of the bone (fig. 4 *C*). The rest of the section, although presenting no area of complete transformation, displayed exceedingly thick trabeculae in the process of much slower resorption and new bone deposition (fig. 6 *B*). Practically all of the haversian systems were bordered by scalloped cement lines. In the less severely transformed area, the diploic spaces contained myeloid and fatty marrow. On the inner surface, the inner ground lamellae were not particularly numerous, while on the outer surface these lamellae were thicker. Thus, this section illustrated a much more intense sclerosis than the one described; it was remarkable in that it presented an area of complete transformation.

Three sections taken from the most compact portions of the calvarium, that is, from the portions showing little if any diploic structure, demonstrated several special features. The compactness had resulted from obliteration of the diploic spaces by new deposits on their walls; the number of haversian systems below the inner and outer ground lamellae had increased considerably; part of the compactness was contributed by new depositions of inner and outer ground lamellae, in most places more prominent on the outer than on the inner side. One of these sections, it is to be pointed out, was from the squama of the temporal bone, which normally tends to show obliteration of the diploic structure. In regard to this bone, the condition was therefore nothing more than an exaggeration of the normal.

In recapitulation, the calvarium evinced several noteworthy features. Although it was, at the most, but slightly thickened, it was much heavier than normal. There was a progressive osteosclerosis in every way similar to the process occurring in the rest of the skeleton. The osteosclerosis was on the whole not associated with scarring of the myeloid marrow. There was deposition of lamellar bone in small irregular fragments; this was the cause of the trabecular thickening.

Furthermore, there was a definite tendency to deposition of new inner and outer ground lamellae; more of the outer ground lamellae was deposited, with apparent cessation of normal resorption on the outer surface of the calvarium. A focus of complete transformation and new bone deposition, associated with the appearance of some fiber marrow, was observed in one of the sections of the parietal bone; this was the only Paget-like focus seen in any of the calvarial sections.[10]

The question naturally arises, How do these calvarial bones differ from the normal? This, of course, presupposes that there are definite standards for the normal calvarium of a man 58 years of age; there are fewer data on the subject than could be desired. One of the chief sources of impediment in making comparisons is the considerable variation even within the so-called normal range. Owing to such variations, precise information on the thickness of the different parts of the calvarium, the thickness of the diploic zone and the appearance of the trabeculae, as well as the appearance and thickness of the inner and outer tables, is lacking. Generally speaking, the calvarial bones reach their full thickness during middle adult life, after which they may normally become somewhat thinner or even thicker. The calvarial thickness of 9 mm. in the case reported is not to be considered extraordinary for a man 58 years of age, as the upper limits of normal are not much shy of this figure. The character of the diploic zone in old age may vary; the diploe may be very extensive and range from plate to plate (this being more common), or they may be considerably reduced in size owing to obliteration (so-called senile osteosclerosis). Bernstein,[11] in a recent study of the normal histologic appearance of the calvarium (which I saw in manuscript), pointed out that in the 51 to 89 year age group there generally is expansion of the diploic zone at the expense of the inner and outer tables, but more largely of the inner table. He further asserted that in this age group the inner

10. The changes observed in the calvarium were different from the calvarial involvement of typical Paget's disease. In such involvement the bones are usually diffusely and uniformly implicated; they may be quite thickened; the occipital bone is likely to be more thickened than the rest. Partial Paget transformation limited to one or more bones of the calvarium is unusual, while a scattered and spotty type had been observed only once by Schmorl.[2] In that instance, the calvarium was not thickened, but numerous circumscribed, somewhat dark, lentil to penny sized foci were observed extending from the outer to the inner surfaces of the calvarium; these showed Paget bone microscopically. The unusual appearance of the calvarium in Pines' case [5] is worthy of mention here as it did not suggest any appearance of Paget's disease either grossly or roentgenographically; it rather suggested Recklinghausen's disease. As regards the Paget nature of the calvarial changes in the case reported, they were the very antithesis of those manifested in Pines' case; they showed generalized sclerosis, rather than porosity.

11. Bernstein, S. A.: Virchows Arch. f. path. Anat., to be published.

ground lamellae are usually much more numerous than the outer ground lamellae. Mair [12] also emphasized the predominance of the inner ground lamellae over the outer ground lamellae in later life. He even denied the possibility that resorption on the inner surface of the inner table occurred except rarely.

It is therefore worthy of note that the sections of the calvarium in the case reported showed, on the whole, a much greater deposition of ground lamellae on the outer surface than on the inner. Furthermore, where the diploic structure existed, the trabeculae were thick, the result of new bone deposition, and, finally, the significant abnormality resides in the construction of the thickened trabeculae by many frag-

Fig. 7.—The iliac bone, about 6 cm. above the upper margin of the acetabulum. The dense sclerosis behind the sacro-iliac joint is observed on the right. The thick trabeculae are evident in the anterior half, to the left.

ments of lamellar bone. The focus of more complete transformation marks the basic nature of the calvarial osteosclerosis.

Innominate Bones: Both of these bones were examined; they were heavier than normal, all prominences being exaggerated; certain portions seemed enlarged. The inner architecture was studied in the gross, by longitudinal sectioning through the acetabulum and horizontal sectioning through the iliac portions. This examination disclosed trabeculae thickened everywhere, with areas of intense sclerosis in the iliac bones behind the sacral articulations. There was a considerable deviation from the normal throughout. The cartilage in the acetabula was degenerated; the attached synovia showed moderate hypertrophy. A horizontal segment was removed from one of the iliac bones, about 6 cm. above the margin of the acetabulum (fig. 7). In the microscopic sections prepared therefrom, all

12. Mair, R.: Ztschr. f. mikr.-anat. Forsch. **5**:625, 1926; Ztschr. f. Anat. u. Entwcklngsgesch. **90**:293, 1929.

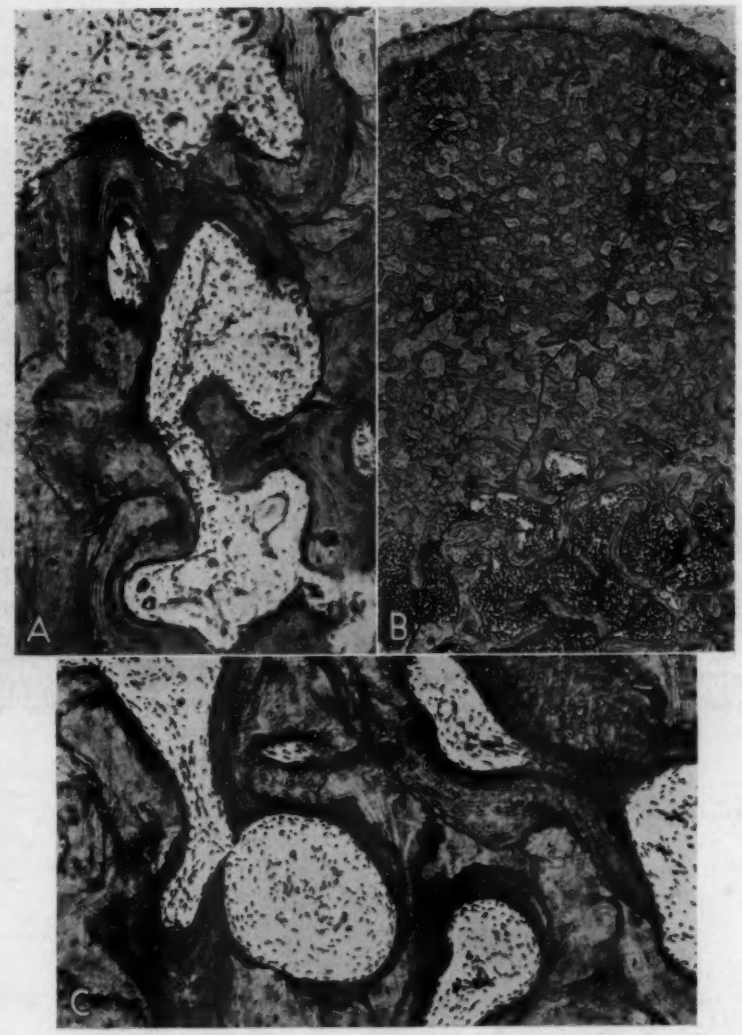

Fig. 8.—*A*, enlarged haversian spaces in the cortical layer of the bone shown in figure 6 *C*. The enlarged spaces contain fiber marrow; new bone deposition is seen on the walls of some of these spaces. Resorption with osteoclasts is observed in other spaces; × 135. *B*, an area below the articular cartilage of the sacral articulation, showing the fiber marrow and newly formed bone in the area of dense sclerosis shown in figure 7; × 5. *C*, the higher power appearance of the bone in the densely sclerotic area shown in *B*. The construction of these newly formed trabeculae of fragments of lamellar bone, separated by thick and short cement lines, gives the appearance of almost typical Paget bone; × 135.

degrees of pathologic change so far described in the various bones of the skeleton were seen concentrated even more intensively.

Sections from the more anterior portions, presenting an outer and an inner cortical layer, showed them to be composed of very compact lamellar bone, with haversian systems extending, in many places, to immediately beneath the periosteum (fig. 6*C*). At one or two points, subperiosteal resorption was observed, but, generally, the striking absence of periosteal activity and periosteal new bone deposition was manifest. Within these cortical layers, a number of haversian canals were greatly enlarged; these canals contained fiber marrow. Some had irregular walls and numerous osteoclasts; others showed definite evidence of new bone deposition, by osteoblasts (fig. 8*A*). The trabeculae throughout, however, were thickened, there being active resorption and new bone deposition. Although these trabeculae were thickened, the marrow was myeloid and fatty where the original trabecular structure was retained (fig. 6*C*).

Somewhat more posteriorly, a section showed much more extensive resorption of the cortex with enlargement and confluence of the haversian systems. The large, confluent haversian spaces were filled with fiber marrow; new depositions on the walls of these spaces could be seen. Although deposited by osteoblasts, this new bone appeared immature and almost identical with fiber bone. The marrow between the thickened trabeculae remained myeloid and fatty. Still more posteriorly, the process as observed in the outer cortex was much more pronounced, and very few of the original haversian systems remained. The depositions of new bone tended to create a Paget-like, mosaic architecture, which reached the typical appearance in the very dense, sclerotic bone observed under the cartilage behind the sacrum (fig. 8*B* and *C*). Some of the marrow between the trabeculae was still myeloid and fatty. In this section, a focus of blue-staining, primitive-appearing bone was seen; it seemed to be hypercalcified bone, in other respects similar to much of the rest of the bone deposited in Paget's disease, when the new depositions are active. About some of the trabeculae, there were wide zones of cells separating the trabeculae from the myeloid and fatty marrow; these cells were fused with the rest of the marrow; they seemed to be modified marrow cells containing no interspersed fat.

COMMENT

In the histologic descriptions, consistent emphasis was laid on certain appearances of the nature of Paget's disease. In the description of the thickened but unreconstructed trabeculae, it was indicated that they presented increased cement lines and were composed of an increased number of fragments (*breccie*) of lamellar bone; on the surfaces of such trabeculae, evidence of resorption and new bone deposition was plainly apparent, although the intervening marrow remained myeloid and fatty. In the locations (areas of dense sclerosis) where the process was apparently much more florid, the myeloid marrow was replaced by fiber marrow and the original bone was replaced by new bone. This new bone was deposited by osteoblasts, was well calcified, was definitely lamellar in part only and contained cement lines, some of which were thick and irregular. Thus, the specialized histologic appearance of the bones in this case was highly suggestive of, without being exactly analogous to, the typical mosaic formation observed in florid Paget's disease.

In the introductory portion of this article, the mosaic architecture that typifies so-called Paget bone was described in some detail; that description pertained to the appearance of the newly formed lamellar bone in the distinctly florid stage of the evolution of the disease. However, the mosaic appearance (on which the histologic diagnosis of Paget's disease depends) is capable of wide variation. The mosaic is most typically constructed in areas of most active disease. The great tendency for spontaneous healing in Paget's disease is associated with regression of the mosaic from the typical. In classic polyostotic Paget's disease, the typical mosaic is to be observed in some bones or in portions of some bones, while healing with regression of the mosaics can be seen in other bones or in other portions of a bone showing florid Paget's disease. Furthermore, when investigation of many bones in a case of polyostotic Paget's disease is made, it may be observed that Paget's disease is capable of evolving more slowly in certain bones. The appearance of extensive mosaic architecture is not evident in any of the bone diseases except Paget's disease. The more florid the disease, the more chaotically are the new lamellar bone fragments arranged, and the more typical the mosaic architecture. Conversely, the more slowly progressive the disease, the more regularly arranged do the new lamellar bone fragments appear, and therefore the less chaotic the mosaic structure. Even in the most florid areas of the disease, the mosaic appearance is to be interpreted as evidence of the initiation of the healing process.

The slow evolution of the pathologic changes in the case reported is the reason for the absence everywhere of a mosaic arrangement such as appears in typically florid areas of Paget's disease. Thus, the slow progress of the disease permitted healing to keep almost apace with its march. For this reason, the cement lines, although more numerous, were on the whole fairly thin and not very irregular; this produced a mosaic architecture not altogether typical compared with that expected in florid disease foci. Even in the densely sclerotic areas, healing kept so close to the changes inaugurated by the disease process that the new bone was well calcified and its mosaic highly suggestive of, but not completely analogous to, that seen in florid disease foci. The slow progress of the evolution of the disease and the concomitant healing were furthermore the reasons why the typical gross appearance of Paget's disease did not manifest itself in this case. Therefore, this is an instance of distinct Paget's disease, peculiar in that slow progress of the pathologic changes permitted healing to keep almost abreast of the evolution of the disease.

The accepted concept of the gross and pathologic anatomy of Paget's disease has not heretofore included a clearcut description of a

form such as this, simulating osteosclerosis. M. B. Schmidt[13] described an apparently similar condition, which he interpreted as osteosclerotic anemia. His subject was a man, aged 56, who had splenomegaly and an anemia that was never definitely classified. During life, he had received radiation therapy for the reduction of an enlarged liver and spleen. The bones showed osteosclerosis (due to new bone deposition on the existing bone and replacement of the myeloid marrow by fiber marrow to the extent of less than one-half). Schmidt stated that the new bone depositions were the result of osteoblastic activity, that osteoclasts were well nigh absent, that the typical mosaic of Paget's disease was not present, and that there were no gross deformities of the bones. He was able to examine the lower half of one femur, and found that while the cortex was not enlarged, the spongiosa was sclerotic and contained a focus of dense sclerosis measuring 2 by 1.5 cm. He was in a dilemma as to the interpretation that could be placed on these changes in the bones, and finally decided that whatever was causing the anemia was producing the changes observed both in the bone and in the marrow. He made it clear that he did not believe that the changes in the marrow were the cause of the anemia.

In searching the literature, Schmidt noted that his case resembled the second and third cases reported by Assmann.[14] It is difficult to be certain of the exact similarity between the changes in the bones in Assmann's cases and in those described by Schmidt. In Assmann's important contribution, the presence of osteosclerosis with leukemia is established beyond doubt; where he discusses anemia and osteosclerosis, no clarity in the histologic descriptions of the changes in the bones exists. It seems to me that since Schmidt himself could not accept the view that the changes in the bones in his case were the result of anemia, and since the anemia was never clearly classified, it may be fair to assume that the anemia was a coincidental feature (the changes in the bones being entirely unrelated to the cause of the anemia). In the case reported here, a moderate secondary anemia existed at the time of the patient's admission to the hospital; there were no particular abnormalities in the red and white blood cells, and since evidences of renal insufficiency were present, sufficient reasons existed for the anemia. Nor did the myeloid marrow, where present (it was not much reduced in amount), appear to show abnormalities. There is no basis in this case for attributing the changes in the bones either to fibrosis of the marrow or to the cause inducing the secondary anemia.

Whether the changes in the bones described are related to the rare endosteal form of Paget's disease which Pick[15] briefly mentioned in

13. Schmidt, M. B.: Beitr. z. path. Anat. u. z. allg. Path. **77**:158, 1927.
14. Assmann, H.: Beitr. z. path. Anat. u. z. allg. Path. **41**:565, 1907.
15. Pick, L.: Klin. Wchnschr. **2**:1044, 1923.

1923 is also difficult to determine. His student, Stenholm,[16] elaborated somewhat more fully on this condition; the cases are listed as cases 11 and 12 in his monograph. Case 11 concerns a boy, 15 years of age, who had sclerotic patches in the tibia and in the fifth lumbar vertebra. In these sclerotic patches, new bone formation was in ascendancy, and osteoclasts were few. The marrow was not particularly congested, nor were there the numerous blood vessels and the large amounts of blood pigment that may be found in the fiber marrow in typical Paget's disease. Case 12 concerned a 17 year old girl. Stenholm concluded that the particular peculiarity of these cases was the atypical localization of the disease to the marrow cavity and the absence of change in form of tubular bones when involved. In 1926, Pick's former assistant, Christeller,[17] in a symposium on fibrous osteodystrophy, again mentioned the endosteal form of Paget's disease. He also stated that in a tubular bone the peculiarity of this lesion is its localization to the marrow cavity, which is filled by a dense, white mass consisting of fibrous tissue and bony trabeculae; similarly, sclerotic foci are to be observed in the vertebrae. These microscopic features were interpreted as evidences of healing, but sufficient details were not given by Pick, Stenholm or Christeller to class these cases absolutely as Paget's disease. Furthermore, the fact that they occurred in young people may be the key to the considerable amount of healing found microscopically. If they are really instances of Paget's disease, the healing tendency may have modified the appearance from the more commonly recognizable manifestation of Paget's disease.

Two more points remain to be discussed: the rôle of chronic nephritis and uremia in influencing the changes in the bones, and the possible influence of lead poisoning (since the subject was a house painter) on these changes. Chronic nephritis is known (under certain circumstances) to induce resorption of bone, so that if it had any effect it was in the direction of increasing the resorption rather than the new depositions. While chronic lead poisoning in infants produces osteosclerosis at sites of most active growth of bone, in adults it appears to have no effect on the bone. Information on this point, however, is rather scant; it is known that in adult dogs chronic lead poisoning does not produce osteosclerosis, while it does so in puppies.

SUMMARY

Bones from a man 58 years of age, showing advanced osteoclerosis, markedly intense in certain areas, were studied. The calvarium, spine, innominate bones, sternum and ribs were investigated; the long tubular

16. Stenholm, T.: Osteodystrophia fibrosa, Uppsala, Almqvist & Wiksell, 1924.
17. Christeller, E.: Verhandl. d. deutsch. path. Gesellsch. **21**:7, 1926.

bones could not be examined. Although Paget's disease was nowhere plainly suggested in the gross, except possibly in the ilia, the microscopic studies led to the conclusion that the changes in the bones were those of Paget's disease. Even the histologic appearances were nowhere similar to the typical mosaic arrangement of florid Paget's disease. It was concluded that the slow evolution of the pathologic changes in the case recorded was the reason for the absence everywhere of a mosaic arrangement such as appears in typically florid areas of Paget's disease. The slow progress of the disease permitted healing to keep almost abreast with its evolution. Furthermore, the slow progress of the evolution of the disease and the concomitantly rapid healing led to the production of osteosclerosis rather than to the usual gross changes of Paget's disease. A somewhat similar case was described by Schmidt, but was erroneously interpreted as osteosclerotic anemia. The relation of this condition to Pick's endosteal Paget's disease is not clear. Thus, Paget's disease may appear in atypical form, the bones, in the gross, evidencing generalized osteosclerosis.

LEIOMYOSARCOMA OF THE DUODENUM

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Eighteen cases of leiomyosarcoma of the small intestine have been reported since 1875. In thirteen of these cases the exact site of origin was mentioned: in ten, the jejunum; in one, the ileum, and in one, the duodenum. It has seemed worth while to report the following case, since it is only the second known case in which the duodenum was involved.

REPORT OF A CASE

A Hungarian machinist, aged 37, was first seen in September, 1927, when he complained of having had tarry stools for seven weeks, and weakness, pallor and palpitations for three weeks. His family, past and personal history was irrelevant. His general health had been good. He appeared well developed, pale and chronically ill. Physical examination gave negative findings except for severe secondary anemia and stools which gave a 4+ response to the guaiac test. A blood count revealed 1,700,000 red blood corpuscles and 6,500 white blood corpuscles. The hemoglobin content was 35 per cent, and the reticulocytes comprised 8.4 per cent. Roentgenograms of the gastro-intestinal tract showed no evidence of a gastric or duodenal ulcer. However, a diagnosis of duodenal ulcer, hemorrhage and secondary anemia was made. The patient was put on a Sippy diet with the addition of liver.

On Sept. 14, 1932, he was readmitted to the hospital with the same complaints. In addition, he had lost weight and had eructations after meals and swelling of the legs and feet; during the previous eight days he had severe squeezing pains in the right leg. Five weeks before this he had first noticed a lump in the right side of the abdomen. He had neither abdominal pains nor fever. There was a moderately tender mass in the right upper quadrant of the abdomen which projected from 3 to 4 cm. below the margin of the liver. This mass was hard and irregular and seemed to be attached to retroperitoneal tissues. There were also a slight dulness at the base of the right lung, with occasional râles and diminished breath sounds, and a slightly enlarged heart, with a systolic blow at the apex. Pitting edema was present in both legs, but was more marked in the right leg.

A blood count showed: hemoglobin, 50 per cent; red blood corpuscles, 3,470,000, and white blood corpuscles, 4,900. The stools gave a negative reaction to the guaiac test. The Wassermann reaction was negative. The urine was normal. Roentgenograms of the colon and abdomen showed a large dense shadow in the right upper quadrant. It was thought that the increased density was due to an abdominal tumor pressing on the colon. The following diagnoses were considered: mesenteric tumor, retroperitoneal tumor and a new growth of the kidney.

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The patient complained of severe pain extending from the right knee downward. Four days after admission he had an attack of dizziness, fainting, palpitation and diaphoresis. Two days later, on September 20, he had a tarry stool; he passed at once into a state of severe shock, and died. The shock was thought to follow an extensive hemorrhage into the gastro-intestinal tract. The clinical diagnosis was: carcinoma of the colon secondary to polyposis (?), secondary anemia due to chronic and acute loss of blood, circulatory failure and shock due to massive hemorrhage into the intestine (probably the colon).

Autopsy.—Four hours after death autopsy was performed. The body was that of a well developed, well nourished, muscular white man, 167 cm. in length. The pupils were equal and regular and measured 6.5 mm. in diameter. The eyes, nose and ears appeared normal. The mouth was in good condition and the neck was normal. The thorax was well developed, with a costal angle of slightly over 90 degrees. The abdomen was flat except for a slight, firm, rounded swelling at the right of the umbilicus. There were no palpable lymph nodes in the inguinal or axillary regions. The extremities appeared normal.

The peritoneal cavity contained no free fluid and was free from infection. The small intestine was pushed into the left lower quadrant by a large, nodular, firm retroperitoneal mass, measuring 15 by 18 by 12 cm. This mass occupied the central portion of the abdomen, extending farther to the right than to the left. The bulk of it lay over and to the right of the upper lumbar vertebrae. The tumor involved the right and posterior aspects of the second portion of the duodenum and the posterior and inferior aspects of the third portion of the duodenum, both of which were pulled down to the level of the lower lumbar vertebrae. The anterior surfaces of the duodenum were free. The mass was also adherent to the lower pole of the right kidney, but there was no involvement of the liver, stomach, spleen, left kidney or suprarenals. The tumor reached to the posterior aspect of the head of the pancreas, but had not invaded its capsule. The colon curved over and around it, but was otherwise normal in appearance. When the duodenum was opened, two ulcerations were found in the region of tumor involvement: one was 8 cm. below the pylorus at the level of the papilla of Vater and measured 3 cm. in diameter; the other was 15 cm. below the pylorus and was a few millimeters in diameter. The margins of these ulcers were firm and irregular; they protruded above the tumor mass and appeared to be continuous with it. At the base the ulcers communicated with large cavities within the degenerated center of the tumor. The larger ulcer led to a cavity 13 cm. in depth, which extended in a diagonal course posteriorly to the right and downward. A section through the tumor showed a hollowed-out mass of tissue, the walls of which were nodular, fairly firm and pale gray. Much necrosis had occurred in the center of the individual nodules. The lumen was occupied by a small amount of thin tarry fluid. Though the mass was adherent to the capsule at the lower pole of the right kidney, it did not appear to involve the tissue of the kidney. It compressed the inferior vena cava, which was otherwise normal. A fairly fresh, firm thrombus occluded the left common iliac vein. The right iliac, femoral and external saphenous veins contained no thrombus. Occluding the right internal saphenous vein and its branches was a pale, friable thrombus, which appeared to be older than that in the left iliac vein.

There were a few fibrous adhesions in the right pleural cavity. The left pleural cavity and the pericardial cavity were normal. The heart weighed 380 Gm. and showed marked dilatation of the right auricle and ventricle and moderate sclerosis of the coronary arteries. The lungs were normal except for the presence

of large masses of thrombotic material in all the large branches of the coronary arteries. The spleen weighed 360 Gm. and was large, soft and deep red.

The liver weighed 2,650 Gm. and measured 30 by 19 by 9 cm. It contained five tumor nodules varying in diameter from 0.5 to 5 cm. They were pale and firm and were outlined by zones of red; the larger ones had soft centers. The bile passages were normal. The common duct extended over the surface of the tumor, but was not obstructed by it. The kidneys were somewhat enlarged. The right kidney was adherent to the tumor mass, but was not invaded by it. The lower portion of the right ureter was compressed by the tumor, with a consequent dilatation of the pelvis of the kidney and the ureter above that point. The pelvic organs were normal. The gastro-intestinal tract, except the portion already described, was normal, and, although the feces in the colon were tarry, there was no evidence of massive hemorrhage. The brain and cord were not removed.

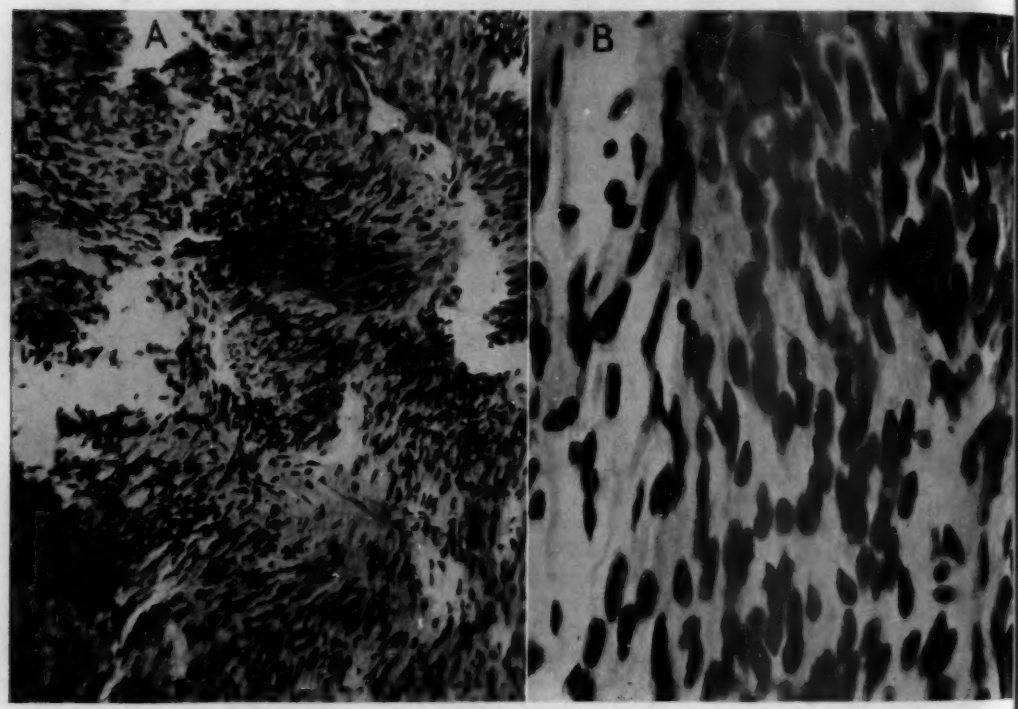
Microscopic Examination.—Section Through the Retroperitoneal Tumor Mass: The tissue consisted of interwoven strands and whorls of spindle cells arranged in irregular palisades and columns. The majority of the nuclei were vesicular and cigar-shaped, though some were pleomorphic and others were long dark-staining rods. Mitotic figures were rare. The intercellular substance was scanty. In places there were infiltrations of plasma cells, lymphocytes and occasional eosinophils. Blood vessels were few, and there were areas of necrosis. These contained extravasated blood, moderate numbers of polymorphonuclear cells and lymphocytes and several large phagocytes which were full of ingested material. The Foote-Bielschowsky stain showed a scanty reticulum, which sometimes surrounded individual cells.

Section Through the Large Duodenal Ulcer: The duodenal mucosa near the margin of the ulcers was edematous, congested and infiltrated with many lymphocytes, plasma cells and eosinophils. Nodules of tumor tissue had infiltrated the muscularis and submucosa. Outside the duodenum the tumor resembled that in the previous section in most places, but other areas were less cellular and had more intercellular collagen. The cells had more cytoplasm and showed much palisading. No capsule was found. There was much necrosis along the surface of the cavity, and numerous lymphocytes and plasma cells were present. A similar infiltration was found in some areas in the tumor tissue. Masson's trichrome stain showed dense collagen and few cells in some regions. Protoplasmic fibrillae could be distinguished in many tumor cells. The phosphotungstic acid stain revealed definite protoplasmic fibrillae in the tumor cells.

Nodules in the Liver: The scalloped margin was sharply defined, and cells resembling endothelial cells surrounded the mass but were separated from it by a sinus-like space containing a fine eosinophilic precipitate. There was no fibrous capsule. The tumor tissue resembled that already described except that it was more cellular and the cells were more rounded. There were areas of degeneration and infiltration by lymphocytes, plasma cells and eosinophils. The adjacent sinuses were engorged. The liver tissue elsewhere contained a moderate number of lymphocytes and polymorphonuclear leukocytes in the portal areas; there was some congestion in the central areas. The phosphotungstic acid stain and the Masson trichrome stain brought out protoplasmic fibrillae in the tumor cells. The Foote-Bielschowsky stain showed a delicate reticulum around each cell in one nodule, while in another nodule the reticulum was rather scanty, but in places surrounded individual cells.

Other Organs: The heart was normal, except for hypertrophy of the muscle fibers and congestion of the capillaries and venules. There was a small lipochrome

deposit at the poles of the nuclei. The aorta showed a slight arteriosclerosis. The lungs showed fresh hemorrhages in many alveoli; these were unaccompanied by any inflammatory reaction in most places. A few alveoli contained small numbers of polymorphonuclears, lymphocytes and eosinophils. The alveolar walls were congested and infiltrated with monocytes, a few lymphocytes and occasional polymorphonuclear leukocytes. The bronchi contained fresh blood. There was moderate emphysema. The pulmonary artery was occluded by thrombotic material, a large portion of which appeared old; the remainder was homogeneous and resembled a propagated clot. The wall of the vessel was disrupted at the point of attachment of the thrombus. The vasa vasorum showed perivascular infiltration



Section from tumor mass: *A*, low magnification; *B*, high magnification.

of lymphocytes, polymorphonuclear cells and monocytes. The spleen presented signs of acute splenic tumor, with extensive hemorrhage into the pulp, congested sinuses and marked infiltration of inflammatory cells, chiefly plasma cells and eosinophils, and also many polymorphonuclears, lymphocytes and phagocytes. No pigment was found. Many fat vacuoles were surrounded by foreign body giant cells. Some of the latter contained ingested droplets of fat. The pancreas, suprarenals, kidneys and pelvic organs were normal. The left femoral vein contained thrombotic material, some of which was old, and some more recent and homogeneous. Organization had begun at one point. The right iliac vein contained no thrombus. Some of the intima lacked endothelial lining, and in this region all layers of the vessel wall seemed disorganized; budding capillaries and young fibroblasts were present, suggesting the beginning of organization of a thrombus.

The anatomic diagnosis was leiomyosarcoma of the duodenum, secondary leiomyosarcoma of the liver, compression of the inferior vena cava, thrombosis of the common iliac veins, pulmonary embolism on both the right and the left and arteriosclerosis of the coronary arteries.

In summary, the features of interest are: a history of duodenal ulcer in a middle-aged man, with repeated intestinal hemorrhages for five years before death; a mass in the right flank, which was first noted only six weeks before death; the finding at autopsy of a large sarcomatous retroperitoneal tumor intimately incorporated in the duodenal wall and ulcerating into the lumen; metastasis to the liver, and a histologic structure of leiomyosarcoma. It is probable that the thrombosis of the common iliac vein was secondary to the compression of the inferior vena cava by the tumor, and the disrupted architecture of the wall of the right iliac vein leads one to suspect that the thrombotic material plugging the pulmonary arteries was originally situated in this vessel. Death followed pulmonary embolism involving all the main branches of both pulmonary arteries.

COMMENT

The only case of leiomyosarcoma of the duodenum in the literature between 1875 and 1933 is that reported by von Salis,[1] in 1920.

In a man, aged 40, the onset was seven years before death. The symptoms were fever, a mass in the abdomen, three fingerbreadths to the left of the umbilicus, and obstipation. There was neither vomiting nor bloody stools. An operation, not described, was performed, which was followed by recovery. Three years after the onset a second operation was performed. The wound drained large amounts of purulent material. During the remaining four years the patient had occasional attacks of fever and diarrhea, which were associated with inadequate drainage from the wound. Another laparotomy was performed, and a large tumor mass was found, into which the fistula opened. There was also a fistulous opening between the drainage tract and the small intestine. The patient survived the operation about four months.

Autopsy disclosed a mass the size of a baby's head attached to the duodenum just above the duodenojejunal junction. It was adherent to the adjacent organs and contained a complicated system of cavities opening into the duodenum and also through the abdominal wound. The cavities contained thick pus and had thick walls. The tumor was lobulated, grayish red and soft in the center. The peritoneal cavity contained 2,500 cc. of thick purulent material, and there was an abscess in the liver. Microscopically, the tumor was composed of spindle-shaped cells. No mitoses were found. The similarity to our case is striking in regard to the age of the patient, the duration of the symptoms, the size of the tumor and the histologic structure.

A third case, that reported by Hültl,[2] might perhaps be included.

A woman, aged 72, had symptoms for several years. An operation was performed, and the patient died two days later. A large tumor was found, which was

1. von Salis, H. W.: Deutsche Ztschr. f. Chir. **160**:180, 1920.
2. Hültl, H.: Deutsche med. Wchnschr. **32**:944, 1906.

thought to have its origin in the muscularis of the duodenum. The tumor infiltrated the pancreas. There was no metastasis. A diagnosis of myoma of the duodenum was made.

From a study of the literature it is evident that leiomyosarcoma of the gastro-intestinal tract is uncommon. According to Corner and Fairbank,[3] the ratio of incidence of myosarcoma of other types in the stomach is 6:52, for the small intestine it is 2:63. According to Speese,[4] this ratio for the small intestine is 1:96. The criteria for the diagnosis of leiomyosarcoma are difficult to apply, since in most cases no special stains were used to establish the presence of myofibrillae and prove the muscle fiber origin, and the malignant nature of the tumors has not always been clearly demonstrated. The diagnosis of malignancy depends largely on the histologic appearance, as the tumors metastasized in only four of the nineteen cases, or 21 per cent, and the tumors tend to grow in bulk in their original site rather than to invade adjacent tissues extensively. Most, however, are not encapsulated. We believe that the diagnosis may be accepted in the cases of Babes and Nanu,[5] Bonneau,[6] Cabot,[7] Cattell and Woodbridge,[8] Demmin,[9] Egtermeyer,[10] Ghon and Hintz,[11] Glass and Alsberg,[12] Kathe,[13] Marwedel,[14] Morpurgo,[15] Richter,[16] Rieckenberg,[17] Steiner [18] and Wortmann.[19]

The incidence of leiomyosarcoma of the small intestine, as shown by the accompanying table, is greatest between the thirtieth and fiftieth year.

Of the eighteen patients whose sex was specified, twelve were men. In the majority of cases the symptoms lasted for from six to twelve months. However, in a case reported by Demmin, no symptoms were

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3. Corner, E. M., and Fairbank, H. A. T.: Tr. Path. Soc. London **56**:20, 1905.
4. Speese, J.: Ann. Surg. **59**:727, 1914.
5. Babes, V., and Nanu: Berl. klin. Wchnschr. **34**:138, 1897.
6. Bonneau, R.: Bull. et mém. Soc. d. chirurgiens de Paris **20**:52 (Jan.) 1928.
7. Cabot, R. C.: New England J. Med. **202**:684, 1930.
8. Cattell, R. B., and Woodbridge, P. D.: S. Clin. North America **11**:363 (April) 1931.
9. Demmin, E.: Aerztl. Sachverst.-Ztg. **18**:76, 1912.
10. Egtermeyer, A.: Inaug. Dissert., Greifswald, 1920.
11. Ghon, A., and Hintz, A.: Beitr. z. path. Anat. u. z. allg. Path. **45**:89, 1909.
12. Glass, E., and Alsberg, J.: Deutsche med. Wchnschr. **48**:1108, 1922.
13. Kathe, H.: Virchows Arch. f. path. Anat. **187**:265, 1907.
14. Marwedel, G.: Beitr. z. klin. Chir. (supp. 7) **24**:104, 1899.
15. Morpurgo, B.: Ztschr. f. Heilk. **16**:157, 1895.
16. Richter, M.: Deutsche Ztschr. f. Chir. **102**:237, 1909.
17. Rieckenberg, H.: Inaug. Dissert., München, 1911.
18. Steiner, R.: Beitr. z. klin. Chir. **22**:407, 1898.
19. Wortmann, W.: Deutsche Ztschr. f. Chir. **123**:103, 1913.

present; death occurred suddenly, preceded by a violent attack of vomiting and by extreme weakness and pallor. In Rieckenberg's case the tumor was an incidental finding in a man, aged 70, who died of heart failure. The symptoms most frequently found were vague abdominal pain (reported in eight), sometimes associated with tarry stools, anemia, palpitation and weakness (reported in eight) and rarely accompanied by vomiting. This is in contrast to gastric myosarcoma, in which vomiting is almost invariably present. Roentgen rays were of but little assistance in the diagnosis of gastro-intestinal myosarcoma, since the growth of such tumors in all but two instances was external to the intestine, and the occasional slight roughening of the mucosal surface was suggestive merely of ulcer. A mass was palpable in only seven cases, facilitating correct diagnoses in these instances. Babes and Nanu,[5] in 1897, reported the first case of leiomyosarcoma of the small intestine

Relation of Incidence of Leiomyosarcoma of the Small Intestine to Age in Cases Reported in the Literature

Age	Number of Cases
1-10	0
11-20	1
21-30	2
31-40	5
41-50	4
51-60	3
61-70	1
71-80	1
Over 80	0
Total	17

which was palpable, and this was also the first case in which a tumor of this type was successfully removed. Richter[16] reported the second case of successful removal of a palpable myosarcoma. Since 1875, six cases have been correctly diagnosed. In one instance the mass was thought to be an ovarian cyst. In nine cases no diagnosis was made.

The size of leiomyosarcomas of the small intestine has varied considerably. The majority reached the size of a baseball; some were the size of a walnut, some the size of a baby's head. Multiple nodules were present in only one case. A tumor of phenomenal size, weighing 7 Kg., was reported by Steiner.[18] In the case reported here the tumor measured 15 by 18 by 17 cm. In some cases the mass grew on a narrow base or stalk. From the reports of the gross structure of these tumors, it appears that they are characteristically hard, coarse, nodular, rather nonvascular structures, prone to degeneration in the center and to ulceration through the mucosal surface of the small intestine. Such ulcerations were described in seven of the nineteen cases. The tumors are usually infiltrating, but are sometimes encapsulated.

Metastases have been reported in only four of the nineteen cases. In the case reported by Ghon and Hintz, there were metastases to the abdominal subcutaneous tissues, thyroid, lungs, liver, pancreas, suprarenals, kidneys, mucosa of the stomach and small intestine and to many bones. In a case reported by Marwedel in a woman, aged 43, a bulky tumor of the jejunum infiltrated the mesentery and metastasized to the regional lymph nodes, right ovary and appendix. Steiner reported the case of massive jejunal tumor in a woman, aged 57, with metastasis to the mesentery. The fourth case with metastases is the one here presented.

In general, lymphosarcoma of the small intestine resembles that of the stomach. Except for its location, the tumor found in our patient is similar to that described by Melnick.[20]

It is likely that many leiomyosarcomas have passed unrecognized, especially before the technic of staining the protoplasmic fibrillae was developed. The literature contains discussions as to the origin of tumors of smooth muscle, their malignancy and their embryonic reversion. Certain microscopic features are, however, common to the cases reported. Most frequent mention was made of the interwoven bundles of spindle cells, usually arranged in columns and palisades, and of the pleomorphism of the nuclei. The majority of the nuclei were rod-shaped, large and hyperchromatic, but multinucleated tumor cells were mentioned in somewhat less than half of the descriptions. Mitoses were relatively rare. The stroma was usually scanty and nonvascular. With Mallory's phosphotungstic acid and Masson's trichrome stains, delicate protoplasmic fibrillae could be demonstrated.

SUMMARY

A case is reported of duodenal leiomyosarcoma with symptoms referable to repeated hemorrhage into the intestine for five years, compression of the inferior vena cava for seven weeks and a palpable tumor in the right side of the abdomen for six weeks. The tumor compressed the inferior vena cava, and thrombi were formed in both common iliac veins. Death resulted from pulmonary embolism. This case and the eighteen other cases of leiomyosarcoma of the small intestine which have been reported in the literature are analyzed.

20. Melnick, P. J.: Am. J. Cancer **16**:890, 1932.

PRIMARY MALIGNANT LYMPHOCYTOMA OF THE PROSTATE GLAND

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Among the rarer malignant tumors of the prostate gland are sarcoma, rhabdomyoma and lymphocytoma. Only eight reports concerning the last-mentioned type are found in the literature (table). Because of the rarity of these tumors this report of lymphocytoma of the prostate gland seems worthy of presentation.

REPORT OF CASE

A ball player and fireman, aged 41, entered the hospital complaining of pain and distress following urination for three weeks. Moderate subacute urinary cystitis of undetermined etiology was found. Examination of the blood showed 100 per cent hemoglobin and a leukocyte count of 9,900, with a normal differential count. The red cells were not counted. The bleeding time and the coagulation time were normal. Nonprotein nitrogen was 42.8 mg. per hundred cubic centimeters; urea nitrogen, 26.6 mg.; sugar, 85.1 mg., and creatinine, 1.2 mg. The Wassermann and Kahn tests were negative. Staphylococci and albumin were found in the urine.

Cystoscopic examination at this time showed obstruction of the prostatic urethra, and the passage of the cystoscope caused bleeding. The bladder was described as inflamed; the prostate, as having an enlarged right lobe. No ulcers or tumors of the bladder were present. Rectal examination disclosed a "hard nodule in the right lobe of the flat, broad prostate." Twenty-six days later an exploratory perineal section was made and the prostate was found "enlarged, firm, thickened and tending to bulge through the capsule when the latter is incised." A portion was removed and the pathologist made a diagnosis of "benign hypertrophy of the prostate with acute and subacute inflammation." The patient remained at rest in bed. Seventy-five days later the physician was unable to pass the cystoscope. Three days after this a suprapubic section revealed a large growth that projected into the bladder. The mass was friable and extended about the meatus. Bleeding was profuse on manipulation. Biopsy at this time revealed a "medullary carcinoma of the prostate." Roentgen examination of the dorsal spine, the ribs and the pelvis revealed no evidence of metastases. The time from the onset of symptoms to death was two hundred and sixty-five days.

Autopsy revealed: primary malignant tumor of the prostate with metastases to the seminal vesicles, bladder, kidneys, mesentery, suprarenal glands, pancreas and capsule of Glisson; bilateral hydro-ureter and hydronephrosis with ascending pyelonephritis on the left side and pyelitis on the right side; emphysema of the lungs; emaciation; a suprapubic cystostomy scar, and a perineal section scar.

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The tumor, with the involved pelvic viscera and the bladder, weighed 1,680 Gm. It measured 13 cm. in the anteroposterior diameter, 15 cm. in the transverse diameter and 16 cm. in the greatest superior-inferior diameter. The capsule was thin. In the subcapsular spaces were numerous diffuse arterial and venous ramifications containing dark red clotted blood. Infiltrating and surrounding the hypertrophied muscle bundles of the urinary bladder were distinct areas of grayish-white new growth. The cavity of the bladder measured 7 cm. in its lateral diameter and 5.5 cm. in its anteroposterior diameter. The base was raised by multiple,

Essential Data on Clinical and Pathologic Manifestations of Lymphatic Tumors of Prostate

Author	Age, Years	Duration	Size	Extension	Metastases	Type
Coupland [8]	29	5 months	8 inches (20.3 cm.) in circumference 3.5 inches (8.8 cm.) in length	Bladder	Pancreas, rib and right suprarenal gland	Lymphoma
Kaufmann: Deutches Clin. **53**: 394, 1902	24½	Not given	Slightly smaller than a fist; frontal plane, 6 by 4.5 cm.	Bladder, posterior portion of urethra and seminal vesicles	Pleura, kidneys, dura, pancreas, cervical lymphatics femur, tibia and cranial vault	Lymphosarcoma
Conforti and Favento: Folia urol. **1**: 180, 1907-1908	45	4 months after operation	7 cm. in height; 10 cm. in width	Bladder, left ureter and urethra	Left kidney	Lymphosarcoma
Quinby [7]*	41	5 months	Not given	Perineum	Brain	Lymphoblastoma
Symmers [5]	30	3 months	9 cm. in diameter; 7 cm. in length	Bladder, seminal vesicles and psoas muscles	Retroperitoneal lymph-glands, kidneys, liver and left pleura	Lymphosarcoma
Bumpus [4]*	28	8 months	Not given	Not given	Not given	Lymphosarcoma
Bumpus [4]*	64	Patient living 2 years after extirpation	Not given	Bladder	Not given	Lymphosarcoma
Zeno, Cid and Ercole: Rev. de cir. de Buenos Aires **10**: 212, 1931*	28	6½ months	Not given	Bladder and posterior portion of urethra	Liver and left inguinal lymph nodes	Lymphosarcoma

* In these instances autopsies were not made. The diagnosis was made on the basis of biopsy.

grayish-white, smooth, glistening nodules which did not rupture the mucosa. The largest of these, to the right of the urethral orifice, measured 2.5 cm. by 1.5 cm. in its various lateral and anteroposterior diameters and extended 1.75 cm. above the floor of the bladder. The posterior portion of the urethra was markedly dilated, and the lumen was invaded by several large polypoid new growths. A midsagittal section of the tumor revealed white, glistening, somewhat rubbery, firm surfaces in which no definite prostatic tissue was observable. The cellular tissue was arranged in large and small islands separated by extremely thin strands of fibrous connective tissue. The muscularis and submucosa of the anterior wall of the rectum were infiltrated with new growth, which, however, did not penetrate the mucosa. The tumor completely invested the seminal vesicles. The small, compressed, yellowish-brown vesicular ducts were sharply demarcated from the surrounding new growth. The lumens of the ducts gave no gross evidence

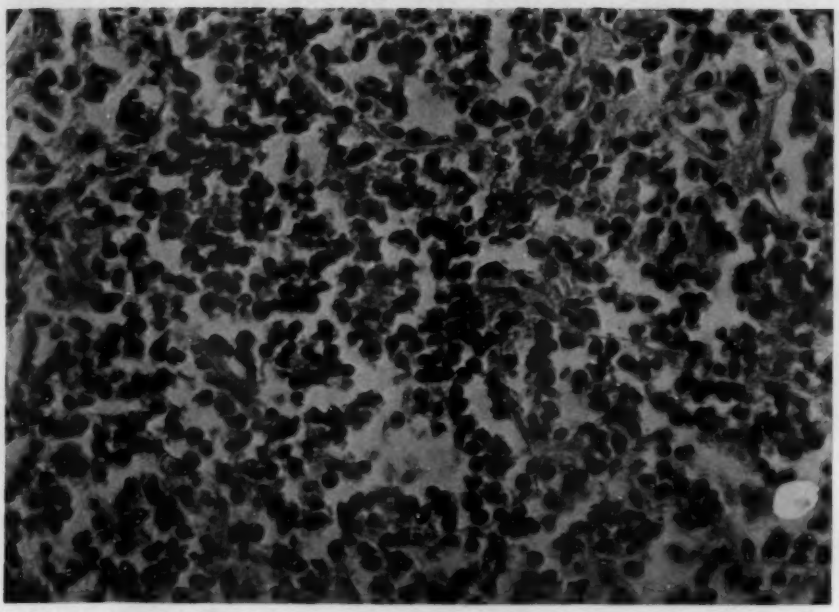

Fig. 1.—Photomicrograph revealing the character of the cells. The poor differential staining is not due to improper fixation since the biopsy specimen showed the same evidence of degeneration.

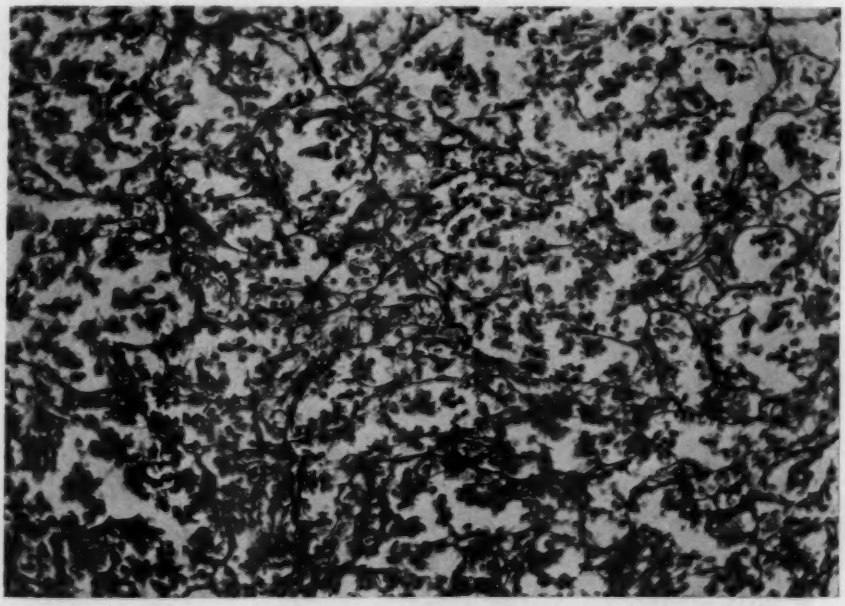

Fig. 2.—Photomicrograph of a metastatic nodule in the pancreas, illustrating the character of the reticulum (Foot's modification of Bielschowsky's stain).

of invasion by the tumor. There was no evidence of cystitis, but the renal pelves contained pus.

Microscopic examination of sections from the center of the tumor showed numerous, closely packed, small, round cells growing diffusely throughout a delicate reticular and vascular stroma (fig. 1). The nuclei were hyperchromatic and from round to oval. The cytoplasm was scant and stained faintly with the acid dyes. Mitotic figures were infrequent. The stroma as seen with special silver stains was composed of fine, threadlike, fibrillar, black strands interwoven diffusely throughout the tissue separating various-sized masses of cells. The delicate fibers anastomosed freely with the single layer of flattened cells comprising the walls of the blood vessels. Sections from the capsular portion of the tumor revealed thin, vascular fibrous connective tissue in which cross-sections of nerve fibers were present. The perineurium here was continuous with many of the small reticular fibrillae that permeated the tumor tissue. The tumor cells were similar to those in the center of the tumor. In neither region was there any observable tendency toward alveolar formation. In the metastases the stroma and cells were similar in type and arrangement to those described.

The predominance of lymphocyte-like cells with a definite reticulum, in the primary as well as in the secondary growths, together with the absence of metastases to the bone and other characteristics of carcinoma led to the conclusion that this was an instance of malignant lymphocytoma of the prostate, although the exact characteristics of the cell type were difficult to determine because of the antemortem degeneration and anaplasia.

COMMENT

The age of incidence of lymphosarcoma of the prostate extends from 24½ to 64 years, the average being approximately 32. Bumpus [1] stated that any neoplasm of the prostate gland occurring before the fortieth year of life should be considered as sarcoma, as his study of one thousand cases of carcinoma of the prostate gland revealed none before this age. Powell [2] pointed out that 25 per cent of the cases of sarcoma occur in persons above the age of 30. The duration of the disease was given in six of the seven reported instances of sarcoma with a fatal termination (table). The most rapidly progressing case was that of Symmers [3] in which the course was only three months. The case reported by Bumpus,[4] which occurred in a 28 year old man, extended over eight months. The average course for the six cases was approximately 5 months. The case reported here was of approximately nine months' duration from the onset of symptoms to death. Individual variations in the rapidity of the course undoubtedly occur, although Smith and Torgeson [5] concluded that the round cell type of

1. Bumpus, H. C.: Surg., Gynec. & Obst. **43**:150, 1926.
2. Powell, R. E.: Canad. M. A. J. **18**:509, 1928.
3. Symmers, D.: Arch. Surg. **6**:755, 1923.
4. Bumpus, H. C.: J. Urol. **14**:519, 1925.
5. Smith, R., and Torgeson, W.: Surg., Gynec. & Obst. **43**:328, 1926.

sarcoma is more malignant than lymphosarcoma. On the basis of the cell type one would anticipate the reverse. The conflict of opinion may be due to inaccuracy of terminology.

In the four cases in which necropsy was performed the prostatic growths varied from 4.5 cm. to 8.9 cm. in height and from 6 to 10 cm. in width, the average height and width being 6.8 and 8.2 cm., respectively. The tumor in the case reported here was large (13 by 15 by 16 cm.). The consistency of a lymphosarcoma of the prostate may be soft and boggy or hard and tense.

The urinary bladder is the most common site of extension; it was involved in six of the eight cases reported. The posterior portion of the urethra was invaded in three instances, and the seminal vesicles were implicated in two. There was definite evidence of invasion of the blood stream in three cases. The para-aortic lymphatics were involved in two of the four cases in which autopsy was performed. In the case recorded here the marked infiltrative growth into the bladder and about the seminal vesicles, as well as the limitation of the metastases to the abdomen, without involvement of the liver or the osseous system, speaks for lymphatic dissemination, although there was no observable implication of the para-aortic chain. Although, as MacCallum [6] observed, lymphosarcoma tends to spread regionally, it is extremely difficult at times to eliminate the possibility of hematogenic dissemination.

With the exception of the case reported by Quinby [7] in which the predominating cell resembled the lymphoblast, none of the other instances of lymphosarcoma of the prostate gland were differentiated as to cell type. In the two cases recorded by Bumpus, descriptions of the predominating cell type were not included. The remaining five cases, including Coupland's,[8] undoubtedly fall into the group of malignant lymphocytoma. The size of the cell is the main point of distinction. In the instance reported here the predominating cell closely resembled the small lymphocyte in size, shape and structure.

The occurrence of primary lymphosarcoma of the prostate was challenged by Ewing [9] on the basis that this gland does not normally contain adenoid tissue and that the so-called lymphosarcoma in reality is nothing more than extremely anaplastic small cell carcinoma. Symmers [3] stated that the prostate belongs to the so-called auxiliary lymphatic system in that it contains interstitial lymphoid foci, which, though often over-

6. MacCallum, W. G.: Textbook of Pathology, ed. 5, Philadelphia, W. B. Saunders Company, 1932.

7. Quinby, W. C.: J. Urol. **4**:137, 1920.

8. Coupland, Sidney: Tr. Path. Soc. London **28**:179, 1877.

9. Ewing, James: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928.

looked, are readily seen in certain conditions. The infrequency of this type of tumor, he explained, is due to the fact that the lymphoid cell rests are numerically insignificant and functionally dormant and undergo hyperplasia only under unusual circumstances. Whether the disturbance in cellular equilibrium is created by bacteria, by their toxins, or by by-products of necrosis is difficult to say. However, in seven of the eight cases of lymphosarcoma of the prostate gland reported in which an adequate abstract of the clinical history was included, there was a history of a preexisting prostatitis in four. This inflammatory condition serving as a continuous source of irritation is accepted as the most probable etiologic factor in epithelial tumors of this organ. There is no reason to suppose that its effect may not occasionally manifest itself on the less frequent, less abundant lymphoid foci as it commonly does on the more numerous, highly functional epithelial cells. That lymphosarcoma may well be primary in this organ seems more certain when one considers that lymphoma of lymphatic leukemia may be found in the prostate (Karsner[10]).

CONCLUSIONS

Lymphosarcoma of the prostate, although rare, should be considered in the differential diagnosis of prostatic tumors.

Lymphosarcoma in this organ probably arises from small, nonfunctional, interstitial lymphoid foci.

Tumors of the type reported usually are large, rapidly growing and of varying consistency, but their histologic structure is relatively constant.

Although lymphosarcoma tends to spread regionally, hematogenic dissemination must be considered.

Malignant lymphocytoma of the prostate gland is more common than large round cell lymphosarcoma or lymphoblastoma.

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10. Karsner, Howard T.: Human Pathology, ed. 3, Philadelphia, J. B. Lippincott Company, 1931.

AVITAMINOSIS

XVI. PRODUCTION OF GASTRIC ULCERS IN THE ALBINO RAT AS A RESULT OF SPECIFIC INFLUENCE OF DEFICIENCY OF VITAMIN B

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In a previous publication Sure, Thatcher and Walker [1] reported that in weaned albino rats deprived of the vitamin B complex the pathologic changes were mainly those associated with inanition. In addition, hypertrophy of the suprarenal glands and of the heart had been observed. In weaned animals suffering from uncomplicated deficiency of vitamin B atrophy of the spleen and hypertrophy of the suprarenal glands and heart were also noted, but the significance of the latter observations was attached to the fact that such changes occurred in animals that were in states apparently uncomplicated by inanition. The dietary regimen, however, was not clearcut for the differentiation between pathologic changes produced by the specific influence of vitamin B and by undernutrition because of insufficient intake of food.

METHODS

In this investigation the dietary technic that was previously described [2] was employed; briefly stated, it consisted in the daily restriction of rats of the same sex, weighing from 40 to 100 Gm., to the same volume of water and amount of food consumed by their litter-mates, which received the diet deficient only in vitamin B or the vitamin B complex; however, in addition, the animals on the restricted diets were allowed vitamin B, either dried baker's yeast incorporated in the ration or a vitamin B concentrate (prepared by one of us, B. S.), separately from the diet. As the plane of nutrition was controlled, the difference in growth and the accompanying pathologic changes produced must be attributed to the specific influence of the B vitamin or the B vitamins, depending on whether vitamin G was furnished in the ration. Thirteen such pairs of experiments were

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1. Sure, Barnett; Thatcher, H. S., and Walker, D. J.: Arch. Path. **11**:413, 1931.

2. Sure, Barnett; Kik, M. C., and Smith, M. E.: J. Nutrition **5**:155, 1932.

employed for the study of the specific influence of the vitamin B complex and eleven pairs for the specific effect of vitamin B on the histologic changes in various tissues.

Four mothers and litters on diets deficient only in vitamin B were also studied, in triads, as follows: Lactating rats were transferred on the day of the birth of their litters, reduced to six, from stock diet 1[3] to ration 1865, which is satisfactory in every respect with the exception of vitamin B content. It is of this composition: casein (purified), 20; salt mixture 185,[4] 4; autoclaved yeast, 10; butter fat, 10, and dextrin, 56. Litter-mates were restricted to the same amount of water and food of the same diet, but the yeast contained in the ration was untreated. The only limiting factor in such a dietary regimen, since the plane of nutrition was controlled, was vitamin B, which was destroyed during the process of autoclaving. Another group of litter-mates was fed the same ration containing 10 per cent of the untreated yeast, but the daily intake of food and water was unrestricted. The difference between the second and third groups must be due to inanition, since the only limiting factor was the plane of nutrition.

In addition, three groups of experiments were studied in quadruplicate so as to determine not only the influence of restricted food but also that of restricted water consumed by the avitaminotic rats.

After the completion of the experiments, the tissues were fixed immediately in formaldehyde. They were stained with hematoxylin and eosin. Practically all of the principal tissues of seventy animals were studied in entirety. These tissues included the heart, lungs, liver, spleen, kidneys, genitalia, suprarenal glands, salivary glands, tongue, pancreas, stomach and intestines. As few changes were found in the seventy animals in addition to those previously reported,[1] fewer tissues were examined in the remainder of the sixty-one animals; in these, observations were made on the heart, lungs, kidneys, spleen, liver and testes.

Records were kept of the body weights of all the animals and of the weights of the liver, spleen, heart, kidneys and suprarenal glands in several groups of animals suffering from deficiency of the vitamin B complex and in several groups of rats suffering from uncomplicated deficiency of vitamin B. These results are given in tables 1 and 2.

RESULTS

The results corroborate the previous findings of Sure and his co-workers[5] that vitamin B not only produces growth by stimulating the appetite, but exerts a specific influence on growth unrelated to the plane of nutrition, in the same sense as certain amino-acids and certain mineral elements exert their influence on growth. As an example of the uncomplicated deficiency of vitamin B, rat 12 ♂ lost 14 Gm. during the experimental period of sixty-three days, and its litter-mate, which was restricted to the same daily amount of food and volume of water, gained 26 Gm. during the same period. Similarly, rat 5 ♂ maintained its weight only during the experimental period of fifty-seven days, while its litter-mate, rat 15 ♂, gained 76 Gm. while on the same daily plane of nutrition.

3. Sure, Barnett: J. Biol. Chem. **69**:65, 1926.
4. McCollum, E. V., and Simmonds, N.: J. Biol. Chem. **33**:63, 1918.
5. Sure, Barnett: J. Biol. Chem. **97**:133, 1932. Sure, Kik and Smith.[2]

TABLE 1.—*Specific Effect of a Deficiency of the Vitamin B Complex on the Weight of the Body, Suprarenal Glands and Organs of the Albino Rat*

P* Animal	R* Animal	Experimental Period, Days	Body Weight: Beginning of Experiment, Gm.	Body Weight: End of Experiment, Gm.	Change of Weight During Experimental Period, Gm.	Weights of Organs and Percentage of Total Body Weight: Liver Weight, Gm.	Liver Per Cent	Spleen Weight, Gm.	Spleen Per Cent	Heart Weight, Gm.	Heart Per Cent	Kidney Weight, Gm.	Kidney Per Cent	Suprarenal Glands Weight, Gm.	Suprarenal Glands Per Cent
6 ♀		41	54	43	— 9	.....	....	0.0850	0.20	0.2598	0.60	0.8918	2.07	0.0080	0.019
	7 ♀	41	53	79	+26	.....	....	0.1730	0.22	0.5132	0.60	0.8566	1.08	0.0210	0.026
8 ♀		68	52	57	+ 5	2.3419	4.24	0.1872	0.31	0.2480	0.43	0.8950	1.57	0.0130	0.025
	9 ♀	68	55	105	+50	5.5390	5.27	0.2230	0.21	0.4818	0.46	1.7080	1.69	0.0183	0.017
10 ♀		73	50	55	+ 5	3.0185	5.48	0.2081	0.38	0.3910	0.71	1.0064	1.82	0.0223	0.041
	11 ♀	73	52	117	+65	4.9962	4.27	0.3722	0.31	0.4949	0.42	1.2600	1.08	0.0352	0.030

* P indicates pathologic; R, restricted to the same plane of nutrition; ♀, female.

TABLE 2.—*Specific Effect of Uncomplicated Deficiency of Vitamin B on the Weight of the Body, Suprarenal Glands and Organs of the Albino Rat*

P* Animal	R* Animal	Experimental Period, Days	Body Weight: Beginning of Experiment, Gm.	Body Weight: End of Experiment, Gm.	Change of Weight During Experimental Period, Gm.	Weights of Organs and Percentage of Total Body Weight: Liver Weight, Gm.	Liver Per Cent	Spleen Weight, Gm.	Spleen Per Cent	Heart Weight, Gm.	Heart Per Cent	Kidney Weight, Gm.	Kidney Per Cent	Suprarenal Glands Weight, Gm.	Suprarenal Glands Per Cent
12 ♂		63	62	48	—14	1.7610	3.67	0.0900	0.19	0.2476	0.51	0.9100	1.90	0.0150	0.031
	13 ♂	63	84	110	+26	4.8551	4.41	0.3230	0.30	0.4772	0.43	1.2000	1.09	0.0196	0.018
4 ♂		53	84	60	—24	1.9403	3.23	0.0834	0.14	0.3000	0.50	0.9610	1.50	0.0236	0.039
	14 ♂	53	97	114	+17	3.7832	3.32	0.4067	0.36	0.4612	0.40	1.1410	1.00	0.0090	0.008
5 ♂		57	55	55	± 0	2.7811	5.05	0.1480	0.27	0.2598	0.47	0.9035	1.64	0.0137	0.025
	15 ♂	57	56	126	+76	5.0300	4.07	0.3300	0.26	0.5000	0.39	1.3400	1.06	0.0166	0.013
6 ♂		59	47	37 D	—10	1.6524	4.57	0.0800	0.22	0.1872	0.50	0.8579	2.31	0.0148	0.040
	17 ♂	59	47	70	+23	3.5200	5.03	0.2550	0.36	0.2970	0.42	1.1342	1.62	0.0231	0.033

* P indicates pathologic; R, restricted to the same plane of nutrition; D, died; ♂, male.

The results of the growth of the animals fed the vitamin B complex are comparable to those cited for the animals fed vitamin B.

The weights of the organs are expressed as percentage of the total body weight. It is apparent that hypertrophy of the suprarenal glands is not the result of inanition, but is due to the specific influence of the deficiency of vitamins, since the weight of the suprarenal glands, as percentage of body weight, is much greater in the pathologic animals than in the restricted controls. In the group fed the vitamin B complex, two of three sets showed hypertrophy of the suprarenal glands due to the specific influence of the vitamin. In this connection, it may be pointed out that the injury produced in animals deprived of all the B vitamins is frequently so severe that the animals die before the investigator has an opportunity to search for and find pronounced chemical or histologic changes. For this reason, it often is advantageous to produce partial instead of complete deficiency of avitaminosis in experimental animals. Animals receiving diets deficient only in vitamin B live for longer periods and in them one often finds considerably more damage, as evidenced by microscopic studies. This was true in the case of our finding of gastric ulcers, as will be brought out later.

An additional point, as is evidenced from an analysis of the weights of the organs, is that a deficiency of vitamin B per se produces hypertrophy of the kidneys.

No specific influence of deficiency of vitamin B is apparent on the weights of the liver and the heart.

Although the histologic analyses indicated atrophy of the spleen in the animals on a restricted diet as well as in the pathologic animals, three of the five groups (as judged by the weights of the organs expressed as percentage of body weight) showed atrophy produced by a deficiency of vitamin B per se.

The animals fed diets deficient in vitamin B and the vitamin B complex, compared with the controls on a restricted diet, showed immaturity of the testes.

Perhaps our most significant result in the investigation is the finding of gastric ulcers as a result of the specific influence of a deficiency of vitamin B.

GASTRIC ULCERS

In 1931 Sure, Thatcher and Walker [1] reported a gastric ulcer in the stomach of a weaned rat suffering from uncomplicated deficiency of vitamin B. Another ulcer was discovered in a recut from some of this material after the article had been published. Ulcers of the stomach were also observed in several polyneuritic, nursing young of the albino

rat.[1] Thatcher, Sure and Walker also reported [6] an ulcer in the rumen of the stomach of a rat suffering from deficiency of vitamin G and a small abscess in the stomach of another rat caused by the same deficiency. However, serial sections were not made because of the extensive technical requirements, and because at that time we were studying many other organs. In the meantime, Dalldorf and Kellogg [7] reported (1932) gastric ulcers in albino rats fed diets deficient in vitamin B. They found 73 per cent of a group with seventy-four observed lesions. Eight of these were chronic, indurated ulcers resembling peptic ulcers in man. It is not apparent, however, from the character of the results of the latter investigators whether the gastric ulcers were produced as a result of inanition or of a deficiency of vitamin B per se. As our control rats were restricted daily to the same plane of nutrition as our pathologic animals, the complication of inanition has been circumvented in our investigation.

Besides the ulcers reported, our experimental work with serial sections of stomachs included those of four rats fed a diet deficient in the vitamin B complex, those of four rats fed a diet deficient in vitamin B and those of eight controls. The entire stomach was mounted, so that the location of the lesion could be obtained. The sections averaged from about 6 to 7 microns in thickness, but those from the controls were from about 15 to 20 microns thick. Every third section was mounted in the stomachs of the animals fed a deficient diet, and all of the sections of the controls were examined. They were stained with hematoxylin and eosin. About 16,000 sections were studied. The animals suffering from a deficiency of the B complex contained no ulcers in the stomach. One of them, however, contained a large cyst between the rumen and the glandular portion in the lesser curvature. The cyst was lined with flattened epithelium, and it was surrounded by a few polymorphonuclear leukocytes.

Serial sections of 4 cm. of duodena from ten rats were studied. These duodena included three from rats on a diet deficient in vitamin B and three from rats on a diet deficient in the vitamin B complex. There were four duodena from control animals. Thousands of sections were examined microscopically, and no duodenal ulcers were found.

A description of the ulcers in the animals fed a diet deficient in vitamin B, including the two in our earlier work, is as follows:

RAT 1 ♂.—An acute ulcer had eroded the glandular portion, but did not involve the muscularis mucosae. The ulcer contained eosinophilic and neutrophilic polymorphonuclear leukocytes, many of which were undergoing degeneration; the

6. Thatcher, H. S.; Sure, Barnett, and Walker, D. J.: Arch. Path. **11**:425, 1931.

7. Dalldorf, G., and Kellogg, M.: J. Exper. Med. **56**:391, 1932.

squamous epithelium was also undergoing degeneration. Fibrin was present. The muscularis mucosa contained a few polymorphonuclear leukocytes, mainly neutrophilic, but occasionally eosinophilic with marked congestion and edema. The same changes were noted in the muscularis. A few small lymphocytes were also present. Near the tip of the ulcer there were keratin flakes and epithelial cells. A small line of dilated vessels and a few polymorphonuclear leukocytes extended into the submucosa (fig. 1).

Rat 2 ♂.—The ulcer was similar to that studied in the stomach of rat 1 ♂, except that it was deeper and there was more cellular débris. It was in the

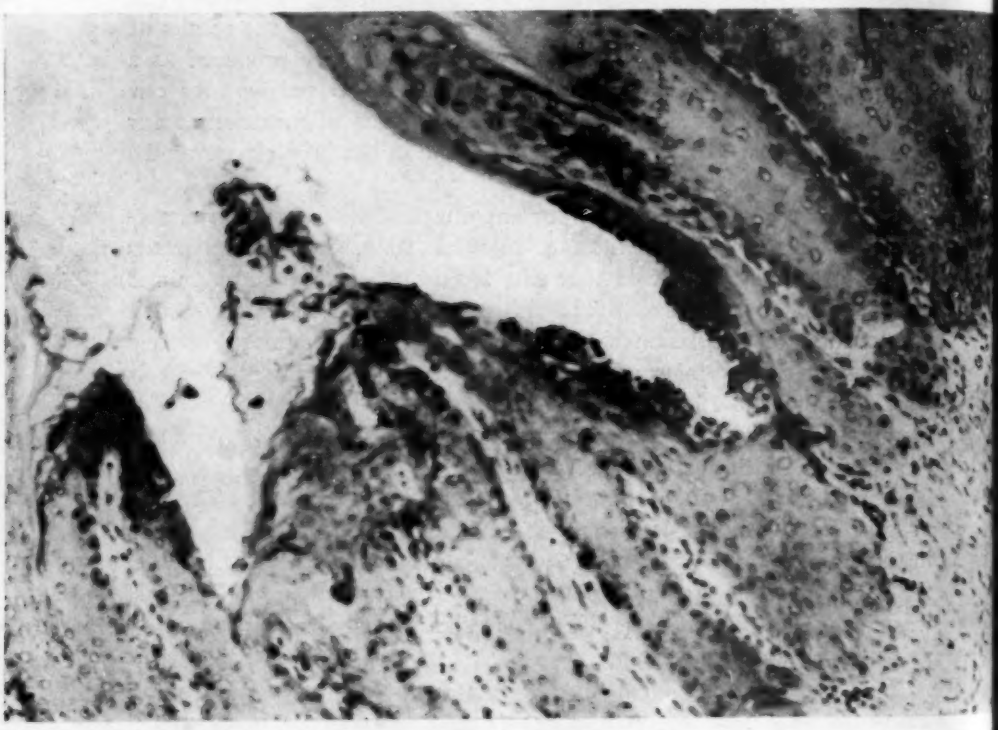

Fig. 1 (rat 1 ♂).—Photomicrograph of an acute ulcer in the glandular portion of the stomach.

glandular portion and extended into the muscularis. The débris consisted of degenerated glandular elements, eosinophilic and neutrophilic polymorphonuclear leukocytes and fibrin. Connective tissue, edema and polymorphonuclear leukocytes were at the base of the ulcer.

The following descriptions are of the ulcers in our later work, containing the serial sections:

Rat 3 ♂.—There was an acute ulcer of the glandular portion in the lesser curvature. It was small and contained polymorphonuclear leukocytes undergoing degeneration; at the base there was a slight amount of fibrin and edema. The

glandular elements were swollen and adherent. At the edges the nuclei were pyknotic. Another smaller ulcer was in the greater curvature at the tip of the glandular portion, but it consisted only of an erosion containing cellular débris and polymorphonuclear leukocytes undergoing degeneration. The third ulcer, which was chronic, extended into the muscularis, even to the outer layer. It was in the lesser curvature and closer to the esophagus than the others. The base consisted of fibroblasts, small lymphocytes and a few eosinophilic polymorphonuclear leukocytes. This portion was edematous. The crater, which was at the lower edge where the rumen should be, consisted of degenerating polymorphonu-

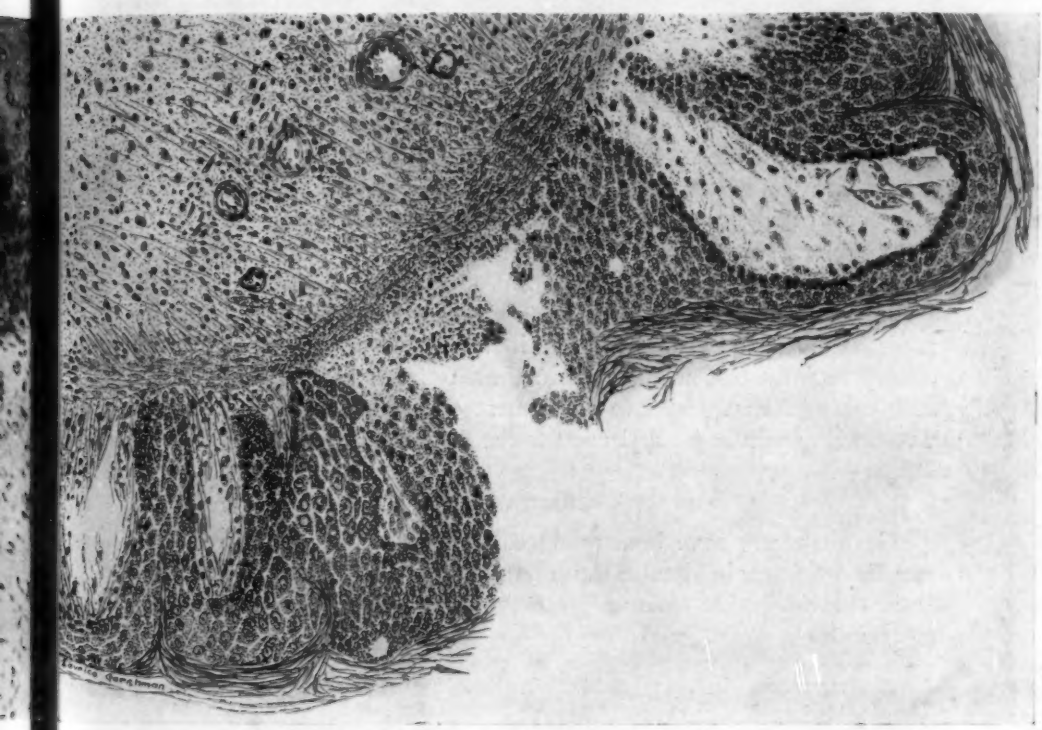

Fig. 2 (rat 3 ♂).—Chronic ulcer in the rumen of the stomach. (Photograph of a drawing.)

clear leukocytes and epithelial cells, as well as fibrin and keratin flakes. New and dilated blood vessels were at the base (fig. 2).

RAT 4 ♂.—The ulcer extended about two thirds of the distance into the squamous epithelium. Red blood cells undergoing degeneration were present, as well as keratin flakes and epithelial cells in the process of degeneration. The ulcer was divided by a region of keratinized epithelium, and the same type of epithelium extended far out over the edge. It was acute and in the rumen at the juncture of the glandular portion about the same distance from the pylorus as from the esophagus. It was in the lesser curvature.

RAT 5 ♂.—A small erosion was present in the glandular portion, extending almost to the muscularis mucosa. It contained remnants of glandular elements, cellular débris and polymorphonuclear leukocytes. It was in the lesser curvature near the pylorus.

Although only five lesions were found in eight rats, the majority occurred in the region of the stomach where they are usually found in man. These microscopic lesions represent acute and one chronic ulcer such as are present in many. The rats with ulcers included in our series were those which were suffering from a deficiency in vitamin B and not from a deficiency of the two vitamins (B and G).

Stimulated by the early work of McCarrison [8] on the production of gastric ulcers in dietary deficiencies, Seale Harris [9] has reported marked success in the cure of gastric and duodenal ulcers with diets abundant in vitamins. It is now apparent from the character of our results and from the recent findings of Dalldorf and Kellogg [7] that a deficiency of vitamin B is one of the causes for the production of gastric ulcers experimentally.[10] Our results, therefore, may be of interest to the gastro-enterologist. Since the diets of patients suffering from chronic peptic ulcers have to be restricted to certain foods that are nonirritating to the gastric mucosa, it is not always possible to select a dietary regimen that will furnish optimum amounts of vitamin B. In such cases it is suggested to experiment clinically with a concentrated vitamin B extract as a supplement to the daily diet.[11]

SUMMARY

Gastric ulcers have been produced in the albino rat as a result of specific deficiency in vitamin B, uncomplicated by the factor of inanition. It is suggested that vitamin B therapy may be indicated in human gastric ulcer.

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8. McCarrison, Robert: Studies in Deficiency Diseases, London, Henry Frowde, Hodder & Stoughton, 1921.

9. Harris, Seale: J. A. M. A. **91**:1452, 1928.

10. That gastric, pyloric and duodenal ulcers may be produced in the guinea-pig by a deficiency of vitamin C has been recently reported by Smith and McConkey (Arch. Int. Med. **51**:413, 1933).

11. Sure, Barnett: The Vitamins in Health and Disease, Baltimore, Williams & Wilkins Company, 1933.

LATENT PORTAL CIRRHOSIS OF THE LIVER

JAMES S. McCARTNEY, M.D.
MINNEAPOLIS

In the literature one finds occasional reference to the accidental finding post mortem of cirrhosis of the liver in persons who had presented no clinical evidence of this disease.

Fagge [1] wrote in 1875: "At the hospital the liver was accidentally found to be cirrhosed in persons who had died of injury or of some other disease once for every two cases in which it had been the cause of death. In many of these cases the organ was indurated in an extreme degree; yet it is certain that the patients suffered from none of the more marked symptoms of such an affection." This conclusion was drawn from the consideration of 130 patients with cirrhosis, and of this number he apparently believed that 58 died of causes other than cirrhosis. Yeld,[2] in 1898, reported 126 cases of alcoholic cirrhosis and found that in 59, or 46.8 per cent, the condition was latent. Candler [3] reported 85 cases from Charing Cross Hospital and 23 from Claybury Asylum. He found that in the former group 12 patients had died as the result of accidents on the street and 10 had died of some intercurrent disease, while in the latter group death was attributed to cirrhosis in but 1 case and none of the 23 patients had ascites. Rolleston [4a] stated:

> Cirrhosis of the liver is not uncommonly latent and does not give rise to any symptoms. It may be found in the bodies of persons who have died as the result of accidents or other diseases. . . . It would be incorrect to say that when a patient dies from some other disease the cirrhosis has necessarily been entirely latent, since patients with cirrhosis rapidly die with pulmonary tuberculosis and are very bad subjects for pneumonia, erysipelas, and other acute infections. The fact, however, that out of 167 consecutive necropsies at St. George's Hospital in which the liver was cirrhotic, 86, or just over half, died from other diseases and not directly from cirrhosis, shows how frequently cirrhosis remains latent.

It appears from the foregoing findings that from 35 to 50 per cent of all cases of cirrhosis are "accidentally" found post mortem. This

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1. Fagge, C. H.: Guy's Hosp. Rep. **20**:155, 1875.
2. Yeld, R. A.: St. Barth. Hosp. Rep. **34**:215, 1898.
3. Candler, J. P., in Mott, F. W.: Arch. Neurol. Path. Lab., London County Asylums **3**:439, 1907.
4. (*a*) Rolleston, H. D., and McNee, J. W.: Diseases of the Liver, Gall-Bladder and Bile-Ducts, ed. 3, New York, The Macmillan Company, 1929, p. 256; (*b*) ibid., pp. 209 and 256; (*c*) ibid., pp. 229 and 230; (*d*) ibid., p. 229.

is a considerable number. One wonders whether it is correct and also whether Rolleston and McNee's statement in the third sentence in the paragraph quoted goes far enough or too far. May it not be that errors are frequently made in the gross diagnosis of cirrhosis? A liver may be called cirrhotic when no cirrhosis is present. For instance, most livers which show fatty metamorphosis are rather friable, but occasionally one is quite firm and cuts with some difficulty and yet is not cirrhotic. In some cases of decompensated heart disease the consistence of the liver seems to be increased, but microscopic examination may nevertheless show no evidence of an increase of the portal connective tissue. Yeld's findings are open to criticism, since no microscopic examinations were made.

Perhaps the incidence of latent cirrhosis would not be so high if in every case all desirable information were at hand, but frequently such data are lacking. Many of the cases in the series reported in this article as latent might have to be shifted into the frankly active group if all the facts were known. It is possible that in many of them there were some symptoms of hepatic disease. The prolonged insidious onset before the appearance of unmistakable signs and symptoms in some cases of cirrhosis is well known. If all the facts were known, perhaps many of these cases should be called compensated, in the sense in which Rowntree [5] used this term, instead of latent.

In 1902, Billings [6] reported 54 cases of what he considered, from a clinical standpoint, to be early cirrhosis. The patients had vague gastro-intestinal symptoms, pains in the muscles, tender, firm, palpable livers and other symptoms. Ascites subsequently developed in 2. Many of them were relieved of their symptoms following the correction of dietary errors and abuses, with reduction in the size of the liver and disappearance of tenderness. That Billings was dealing with cases of early or potential cirrhosis cannot be determined; he did not represent the cases as proved but rather as suggestive.

There is marked variation in the incidence of cirrhosis in different parts of the world. Yeld,[2] for instance, found 164 cases in 4,117 necropsies; Candler [3] found 85 in 1,099 postmortem examinations at Charing Cross Hospital and 23 in 1,271 postmortem examinations at the Claybury Asylum. Blumenau,[7] in 12,761 necropsies, found 126 cases in which a macroscopic diagnosis of cirrhosis was made and 64 additional cases in which the diagnosis was made microscopically.

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5. Chapman, C. B.; Snell, A. M., and Rowntree, L. G.: J. A. M. A. **97**:237, 1931.

6. Billings, F.: Tr. A. Am. Physicians **17**:611, 1902.

7. Blumenau, E.: Arch. f. Verdauungskr. **27**:1, 1920.

Rössle [8] collected statistics published in different parts of the world, which show an incidence varying from 0.85 to 5.5 per cent. In this laboratory there were 245 microscopically proved cases of portal cirrhosis in 11,912 necropsies performed on adults, or an incidence of 2.05 per cent. The type of material available in different laboratories, even in those which are closely related geographically, doubtless varies tremendously. The material studied in this laboratory came from three large charity hospitals, a large number of private hospitals in Minneapolis and St. Paul, the coroner's service and the private practice of physicians.

All the cases recorded during the period from 1910 to 1931, inclusive, in which a gross diagnosis of cirrhosis was made post mortem and in which material was available for microscopic examination, have been studied. In some instances only a single section was preserved; in others, blocks of tissue, and in still others, the liver. An effort was made to obtain, so far as possible, sections from representative areas of each liver.

Some of these cases have been excluded because on microscopic examination there did not appear to be sufficient evidence of proliferation of connective tissue or of the bile ducts to substantiate the gross diagnosis. In this article all cases which occurred in patients under 20 years of age and all cases of pure hepar lobatum, obstructive biliary cirrhosis and definitely acute yellow atrophy were excluded.

Sections from the 245 livers were carefully studied and were divided into three groups according to the degree of cirrhotic change present. The determination of the degree of cirrhosis in each case was made independently of all clinical and postmortem information; i. e., it was based on what the sections alone showed. In many instances it was necessary to be rather arbitrary in deciding to which of the three groups a given liver should be assigned. The series showed a gradual transition from the slightest changes compatible with a diagnosis of cirrhosis to the most extreme fibrosis and distortion of the hepatic structure. In some livers different degrees of the process were found in different sections. Photomicrographs *A*, *B* and *C* (fig. 1) are type specimens illustrating the three degrees.

Sears and Lord [9] made a somewhat similar division into four classes of a series of 78 cirrhotic livers, and placed 4 in class 1, 16 in class 2, 35 in class 3 and 23 in class 4. Only 8 of their cases were classed as latent cirrhosis.

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8. Rössle, R., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1930, vol. 5, pt. 1, p. 284.

9. Sears, G. G., and Lord, F. T.: Boston M. & S. J. **147**:285, 1902.

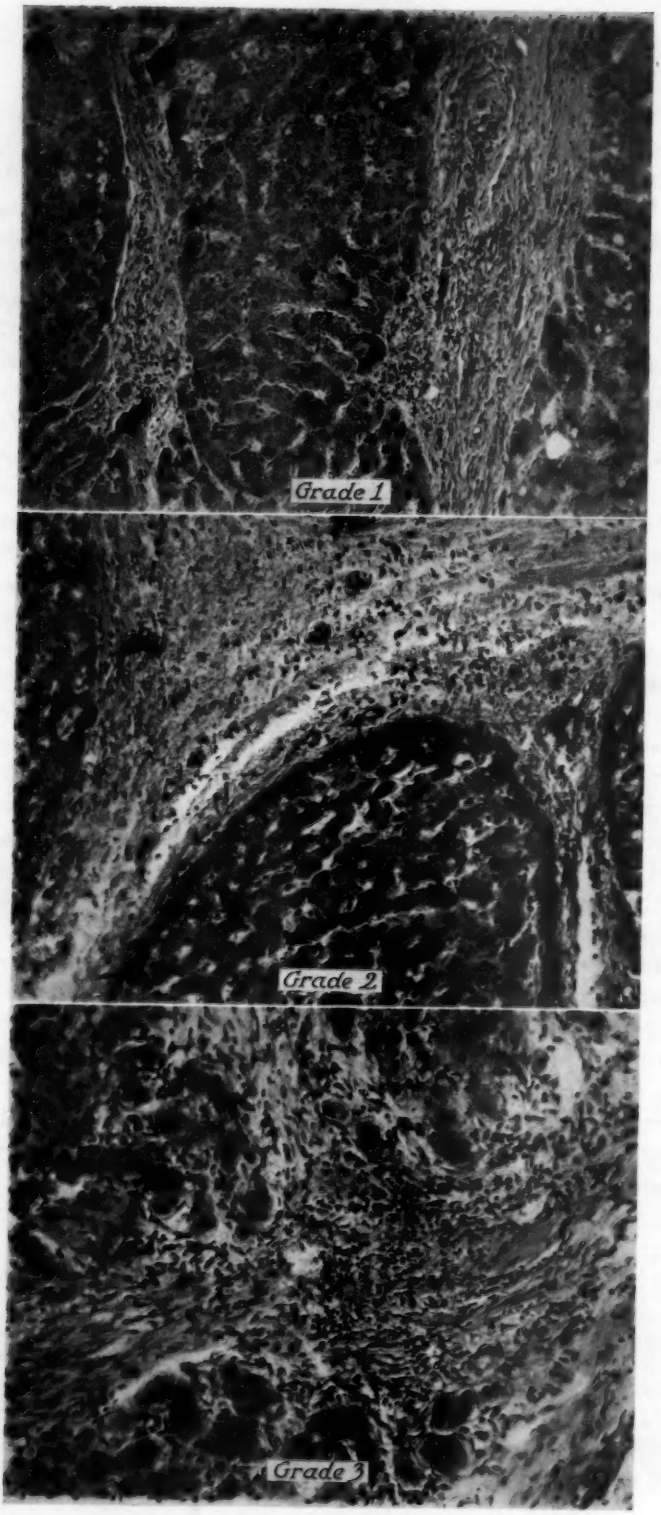

Fig. 1.—Photomicrographs showing degrees of cirrhosis; × 145.

In this study the diagnosis of cirrhosis was established by microscopic examination of the liver, and the cases were then separated into active and latent groups on the basis of the clinical data and postmortem observations. Microscopic changes in the liver were not considered in separating the active and latent cases. All cases were considered active in which there was any clinical evidence of the disease, such as gastric hemorrhage, jaundice, ascites, varices or gastro-intestinal disturbances. Cases were also considered active if postmortem examination revealed jaundice, ascites or esophageal varices, even though hepatic disease was not suspected clinically. Since the clinical history was often incomplete, it is probable that some of the cases which were classified as latent really belong to the active group. In the presence of definite cardiac decompensation, ascites was considered to be of cardiac origin. In several instances an associated disease, such as carcinoma of the stomach, made it difficult to decide whether the symptoms were of hepatic origin.

DISTRIBUTION OF CASES

As a result of this analysis, 158 of the 245 cases were classified as active and 87 as latent; i. e., 64.4 per cent were active and 35.5 per cent latent. These percentages agree with those of Fagge.[1]

In the latent group, 76 of the patients were males and 11 were females, a ratio of 6.9:1. In the active group there were 110 males and 48 females, or a ratio of 2.2:1. Considering the 245 cases as a whole, there were 186 males and 59 females, or a ratio of 3.1:1.

Fagge stated: "The proportion of males to females appears from the records at the hospital to be 102 to 26, or very nearly as 4 to 1." Price[10] found that of his group of 142 patients 26 per cent were females, a ratio of approximately 3:1. In Yeld's[2] group there were 102 males and 29 females. This is almost identical with the ratio in Fagge's group. In Candler's[3] group there were 91 males and 27 females, a ratio of 3.3:1. Rolleston and McNee[4b] gave the ratio as "about 3 to 1." Their ratio was apparently arrived at from collected statistics, including those cited here.

However, the ratio of males to females in this series needs to be corrected. In the postmortem service of this laboratory the ratio of males to females between the ages of 20 and 89 years is almost exactly 2:1 (10,920 necropsies; 7,293 males, 3,627 females). When this fact is considered it is found that for the latent group the ratio becomes 3.5:1, for the active group, 1.1:1 and for the whole series, 1.5:1. This indicates only a moderate preponderance of males and bears out the statements of Yeld[2] and of Rolleston[4a] that cirrhosis is latent more often in males.

10. Price, J. A. P.: Guy's Hosp. Rep. **27**:295, 1884.

Fagge [1] found that the average age of the patient with latent cirrhosis at the time of death was about five years greater than that of the patients who died of active cirrhosis. According to Yeld, the average age in the latent group (56 patients) was 48.9 years and in the active group (56 patients) 46.5 years. Sears and Lord [9] found that the patients with latent cirrhosis were about two years older than those with active cirrhosis. Fagge also found that the greatest number of patients with active cirrhosis died between the ages of 40 and 50 years. In the series described in this article the average age in the latent group was 55.8 years, and in the active group, 54.3 years. However, to state an average age for this group is misleading, since only adults were considered. The distribution according to decades gives a clearer conception of the time of life when patients with cirrhosis of the liver are seen.

TABLE 1.—*Distribution of Cirrhosis According to Age and Sex*

Age, Years	Latent Cases			Active Cases		
	Males	Females	Per Cent	Males	Females	Per Cent
20–29	5	0	6.0	2	2	2.7
30–39	5	0	6.0	12	7	12.8
40–49	12	2	17.0	16	9	16.8
50–59	20	3	28.0	33	11	29.7
60–69	18	3	25.6	22	11	22.2
70–79	9	1	12.1	16	6	14.8
80–89	3	1	4.8	0	1	1.4
Adults, age unknown	4	1		9	1	
Total	76	11		110	48	

It may be noted from table 1 that the maximum incidence of both latent and active cirrhosis is in the sixth and seventh decades. Practically 70 per cent of both groups of patients were between the age of 40 and 69 years. The incidence in the third and fourth decades is approximately the same as in the eighth and ninth. The difference in age in the two groups is practically negligible. It is worthy of mention that of 5 cases of cirrhosis in persons over 80 years of age, only 1 was the active type.

The simple numerical distribution of this series of cases, according to sex, age, degree of microscopic change and the presence or absence of symptoms indicates a great variation in the frequency of the process in corresponding decades. This variation is probably the result of the large error introduced by subdivision into so many small groups. By using percentages instead of actual numbers and by eliminating sex, a different impression is obtained. This distribution has been made in two ways: first, by considering the latent and active groups separately (table 2) and, second, by considering the series as a whole (table 3).

From a study of table 2, it is evident that in both the latent and the active type the greatest incidence is in the sixth decade, 27.9 per cent

of the latent cases and 29.5 per cent of the active group being found here. It is also to be noted that in the latent group the highest percentage is in grade 1 cirrhosis, whereas in the active type the highest percentage is in grade 3 cirrhosis, and that in each instance this is in the sixth decade. There is no evidence that the more advanced degrees of cirrhosis were more frequent in the older patients. It does not appear

TABLE 2.—*Percentage Distribution of Latent and Active Cirrhosis of Each Type According to Age and to Degree of Microscopic Change*

	Latent Cases				Active Cases			
	Degree of Change			Total Number	Degree of Change			Total Number
	1	2	3		1	2	3	
Number of cases	35	28	19	82	23	32	93	148
Age, Years								
20-29	2.4	1.2	2.4		1.3	0.0	1.3	
30-39	1.2	3.6	1.2		0.6	3.3	8.7	
40-49	4.8	3.6	8.5		2.7	1.3	12.8	
50-59	12.2	10.9	4.8		3.3	6.7	19.5	
60-69	9.6	10.9	4.8		3.3	4.7	14.8	
70-79	10.9	1.2	0.0		4.0	4.7	5.4	
80-89	1.2	2.4	1.2		0.0	0.6	0.0	
Per cent	42.3	33.8	22.9	99.0	15.2	21.3	62.5	99.0
Adults of unknown age	2	1	2		2	2	6	

TABLE 3.—*Percentage Distribution of Both Types of Cirrhosis According to Age and to Degree of Microscopic Change*

	Degree of Change						
	1		2		3		
	Latent Type	Active Type	Latent Type	Active Type	Latent Type	Active Type	Total Number
Number of cases	35	28	19	23	32	93	230
Age, Years							
20-29	0.8	0.8	0.4	0.0	0.8	0.8	3.6
30-39	0.4	0.4	1.3	2.1	0.4	5.6	10.2
40-49	1.7	1.7	1.3	0.8	3.0	8.2	16.7
50-59	4.3	2.1	3.9	4.3	1.7	12.6	28.9
60-69	3.4	2.1	3.9	3.0	1.7	9.5	23.6
70-79	3.9	2.6	0.4	3.0	0.0	3.4	13.3
80-89	0.4	0.0	0.8	0.4	0.4	0.0	2.0
Total per cent	14.9	9.7	12.0	13.6	8.0	40.1	98.3

from this table that if the persons with latent cirrhosis had lived long enough, active cirrhosis would have developed eventually. The totals, both numerically and from the standpoint of percentages, in each degree of latent cirrhosis show a progressive decrease as one passes from the least advanced to the most advanced process. The converse is true of active cirrhosis; i. e., there is a progressive increase in the totals in each degree as one passes from grade 1 to grade 3 cirrhotic change. In the age period 50 to 79 years the percentage distribution within each type is as follows: grade 1 cirrhosis, 32.7 per cent latent and 10.6 per cent

active; grade 2 cirrhosis, 23 per cent latent and 16.1 per cent active; grade 3 cirrhosis, 9.6 per cent latent and 39.7 per cent active. If one considers grade 3 cirrhosis in the period of from 40 to 69 years of age, one sees that here will be found 18.1 per cent of the cases of the latent type and 47.1 per cent of the cases of the active type. This appears to indicate that latent cirrhosis does not tend to progress into the active form. The latent type either progresses more slowly or tends to become arrested. It is also apparent that in latent cirrhosis there is often a lower degree of microscopic change than in the active form; 75.8 per cent of the cases of latent cirrhosis showed grade 1 or 2 change, whereas 62.6 per cent of those of active cirrhosis showed grade 3 change.

Table 3 carries this analysis one step further. In this table it appears that in the first two degrees the percentage distributions for corresponding decades agree fairly well, but that agreement is not present in third degree cirrhosis. It is to be noted that 40 per cent of the 230 cases in which a definite age was given are found in the grade 3 active group, whereas only 8 per cent fall within the grade 3 latent group.

The foregoing findings indicate that the degree of cirrhosis is one of the factors in latency, although many patients who suffer from the disease have only a mild degree of cirrhotic change. Further, it appears that high degrees of cirrhosis are but rarely unaccompanied by symptoms.

After these tabulations were made in all cases classed as grade 1 the sections were reexamined to determine whether the presence of so-called adenomas could be responsible for the fact that so many cases had been placed in this group. Reexamination showed that in 2 cases of active cirrhosis and in 1 of latent cirrhosis such a relobulation was present. In the remainder no evidence of adenoma was found. Thus it appeared that regeneration was responsible for neither the slight degree of microscopic change nor the latency of the disease.

OBSERVATIONS ON THE WEIGHT OF THE LIVER

The microscopic changes in the cirrhotic livers having shown such great variations, a study was made of the weights of the livers, since not all could be examined grossly. A tabulation of these weights is shown in table 4. (Boyd,[11] using the records of this laboratory, recently reported on the weight of the normal liver and of the normal spleen. She showed that there is a significant difference in weight according to sex and also that these organs decrease in weight with advancing age. The normal averages for the various decades used in this table were furnished by her.) From this table it appears that, although there is

11. Boyd, E.: Arch. Path. **16**:350, 1933.

considerable variation in each decade between the maximum and minimum weights of cirrhotic livers, there is a decided decrease in the maximum and average weights with advancing age. It is to be noted that the weight of the liver decreases with age in the normal cases also. The decrease in the average weights for the successive decades in the latent cases in males shows no great variation from the normal. In some of the decades the cases are so few that no conclusion can be drawn. The decrease in weight with advancing age is decidedly greater in the cases of active cirrhosis than in the normal group. In the fourth, fifth and sixth decades in the cases of the latent group and in the fourth and fifth decades in the cases of the active group there may be a signifi-

TABLE 4.—*Comparison of the Weights of Cirrhotic Livers with the Normal Averages According to Sex, Age and Maximum, Minimum and Average Weight (Gm.)*

Age, Years	Males					Females				
	No. of Cases	Maximum Weight	Minimum Weight	Average Weight	Boyd's Normal Average	No. of Cases	Maximum Weight	Minimum Weight	Average Weight	Boyd's Normal Average
Latent Cirrhosis										
20–29	4	1,700	1,185	1,332	1,838	..	.....	.....	.....	1,437
30–39	5	2,922	1,380	2,156	1,872	..	.....	.....	.....	1,462
40–49	11	3,530	1,250	2,156	1,888	2	1,601	1,390	1,495	1,570
50–59	18	3,792	1,050	1,996	1,848	3	2,800	1,592	2,097	1,464
60–69	15	2,713	720	1,729	1,728	3	2,100	1,390	1,780	1,400
70–79	9	2,100	1,007	1,419	1,426	..	.....	.....	.....	1,263
80–89	2	1,650	1,500	1,575	.....	1	.....	987	987	.....
Active Cirrhosis										
20–29	2	1,550	1,400	1,475	1,838	2	3,025	2,560	2,792	1,437
30–39	11	3,080	1,097	2,092	1,872	7	3,140	875	1,751	1,462
40–49	16	3,400	940	1,999	1,888	6	3,100	880	2,144	1,570
50–59	29	2,500	750	1,452	1,848	8	2,391	650	1,282	1,464
60–69	22	2,300	750	1,305	1,728	10	1,625	675	1,130	1,400
70–79	15	2,100	675	1,365	1,426	5	1,100	625	767	1,263
80–89	..	.....	.....	.....	.....	..	.....	.....	.....	.....

cant increase in the weights of cirrhotic livers in males. This analysis does not entirely confirm Rolleston and McNee's [4c] statement that there is a decrease in the size of cirrhotic livers with advancing age.

The following data do not appear in the table. In the latent group only 2 patients, 1 male and 1 female, had livers weighing less than 1,000 Gm. In the active group, on the other hand, 16.5 per cent of the males and 43.5 per cent of the females had livers weighing 1,000 Gm. or less. It is unlikely that this high incidence of very small livers found in females with active cirrhosis can be attributed entirely to sex, which agrees with Rolleston and McNee's [4c] statement that "sex does not exert any very special influence on the weight of the cirrhotic liver."

In figure 2, the weights of the livers in the cases of latent cirrhosis have been plotted on the standard of normal variability in the weight of the liver, constructed by Boyd, in which the dispersion of normal weights is divided into the eight zones indicated. The number of

weights which normally should fall below any given line is indicated in percentages at the end of each line, and the number expected in each zone would be the difference between its limiting percentile lines. The number of weights of cirrhotic livers found in each of the eight zones is shown in percentages in table 5. A count of the numbers of weights in each of the eight zones shows that 13.6 per cent are found above the 97.5 percentile line, where only 2.5 per cent are expected normally, and, likewise, that 13.6 per cent are below the 2.5 percentile line. Apparently the liver may be either hypertrophied or atrophied. This conclusion is supported by finding that such deviations in normal weights from the expected standard would not occur by chance alone once in a million times, since Chi-square is 91.5 and P is 0.000000 (Boyd[11]).

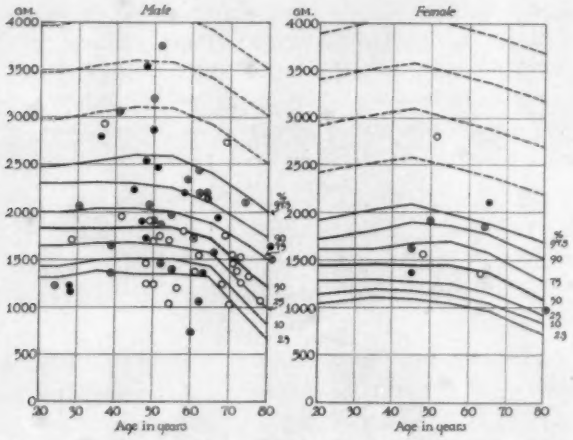

Fig. 2.—Dispersion of the weights of the livers in the cases of latent cirrhosis, plotted on the standard of normal variability in weight. In this and in the following charts the white circles indicate grade 1 cirrhosis, the white circles with the black centers, grade 2, and the black circles, grade 3.

Inspection of the graph indicates that in latent cirrhosis the liver tends to be hypertrophied oftener in the early decades of adult life and atrophied oftener in the later decades. Therefore the incidence of weights was divided into two groups at 50 years of age. This division shows that the percentage of weights above and below the probable limits of normal variation remains equal in both groups: it is 17.4 for the period of from 20 to 49 years and 12 for the period of from 50 to 89 years. Here again, the liver may be hypertrophied or atrophied, regardless of age. This statement is supported by finding that such deviations in normal weights from the expected standard would not occur by chance alone once in a million times, since in the earlier decades Chi-square is 45.6 and P is 0.000000, and in the later decades Chi-square is 57.7 and P is 0.000000.

TABLE 5.—*Comparison of the Weights of Cirrhotic Livers with the Normal Standard* *

	Number of Weights (Both Sexes)	Percentage of Weights Between the Percentile Lines											Percentage of Weights	
		Above 97.5 Line	97.5 to 90	90 to 75	75 to 50	50 to 25	25 to 10	10 to 2.5	Below 2.5 Line	n′	χ^2†	P	Above 50 Line	Below 50 Line
Percentage of weights expected.....	..	2.5	7.5	15	25	25	15	7.5	2.5	...	....	.....	50	50
Latent cirrhosis	73	13.6	15.0	8.2	16.4	20.5	2.7	9.5	13.6	8	91.5	0.000000	53.4	46.5
20-49 years	{23	17.4	4.3	13.0	21.7	13.0	4.3	8.6	17.4	8	45.6	0.000000	56.5	43.4
50-89 years	{50	12.0	20.0	6.0	14.0	24.0	2.0	10.0	12.0	8	57.7	0.000000	52.0	48.0
Active cirrhosis	133	12.0	8.2	4.5	13.5	9.7	6.0	9.0	36.8	8	716.3	0.000000	38.3	61.6
20-49 years	{44	31.8	15.9	2.2	11.3	4.5	9.0	6.8	18.1	8	215.2	0.000000	61.3	38.6
50-89 years	{89	2.2	4.4	5.6	14.6	12.3	4.4	10.1	46.0	8	698.9	0.000000	26.9	73.0
		Above 75 Line		75 to 50		50 to 25		Below 25 Line						
Percentage of weights expected.....	..	25		25		25		25		...	....	....	50	50
Latent cirrhosis	73	36.9		16.4		20.5		26.0		4	6.9	0.07	53.4	46.5
20-49 years	{23	34.7		21.7		13.0		30.4		4	3.4	0.40	56.5	43.4
50-89 years	{50	38.0		14.0		24.0		24.0		4	5.8	0.10	52.0	48.0
Active cirrhosis	133	24.8		13.5		9.7		51.8		4	57.9	0.000000	38.3	61.6
20-49 years	{44	50.0		11.3		4.5		34.0		4	23.6	0.000025	61.3	38.6
50-89 years	{89	12.3		14.6		12.3		60.6		4	60.3	0.000000	26.9	73.0
		Above 50 Line				Below 50 Line								
Percentage of weights expected.....	..	50				50				...	....	....	50	50
Latent cirrhosis	73	53.4				46.5				2	0.34	0.60	53.4	46.5
Active cirrhosis	133	38.3				61.6				2	7.2	0.01	38.3	61.6
20-49 years	{44	61.3				38.6				2	2.2	0.10	61.3	38.6
50-89 years	{89	26.9				73.0				2	18.8	0.000000	26.9	73.0

* Sex has been eliminated in this table, since the cases found in the corresponding zones may be added together without introducing an error.
† When less than ten weights are expected in a zone the interpretation of the χ^2 tests is not highly reliable.

As the samples are so small that less than ten weights are expected normally in the extreme zones, the counts were grouped first into the four quartiles and then into the number above and below the median line (table 5).

The count of the number of weights in the quartiles for the total age period and its two divisions indicates that a disproportionate number of weights are in the upper quartile (36.9, 34.7 and 38 per cent) and about the expected number are in the lower quartile (26, 30.4 and 24 per cent), but the Chi-square values 6.9, 3.4 and 5.8 are so low that these differences could occur by chance alone 7, 40 and 10 times, respectively, in a hundred. In short, about the usual number of weights are in the two middle quartiles, and the usual number are outside. However, this test

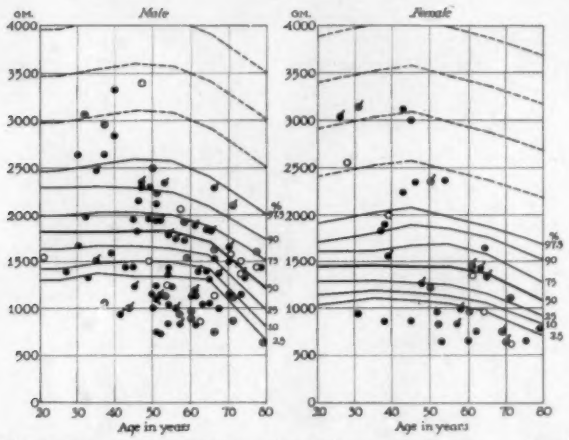

Fig. 3.—Dispersion of the weights of the livers in the cases of active cirrhosis, plotted on the standard of normal variability in weight. The circles with the dashes indicate the cases in which hemorrhage occurred.

gives no indication of how far the weights in the fourth quartile are above the 75 percentile line or how far those in the first quartile are below the 25 per centile line. Likewise, since the numbers below and above the median line, 53.4 and 46.5 per cent, could occur by chance 60 times in one hundred, this dispersion is obviously not different from the number of normal weights above and below the median. Therefore the number of hypertrophied and atrophied livers counterbalance each other so that the median weight in latent cirrhosis is not significantly different from that of the normal liver.

The weights of the livers in the cases of active cirrhosis were plotted on the normal standard (fig. 3). The count of the number of weights in each of the eight zones shows that 12 per cent are above the 97.5 percentile line and 36.8 per cent are below the 2.5 percentile line, when in each case only 2.5 per cent are to be expected normally (table 5). As

in latent cirrhosis, the liver may be hypertrophied or atrophied. Support for this conclusion is found in the fact that such deviations in normal weights from the expected standard would not occur by chance once in a million times, since Chi-square is 716 and *P* is 0.000000.

Examination of the graph indicates that in active cirrhosis the liver tends to be hypertrophied oftener in the early decades of adult life and atrophied oftener in the later decades. As in latent cirrhosis, the incidence of weights in active cirrhosis was divided into two groups at the age of 50 years. This division shows that for the age period of from 20 to 49 years 31.8 per cent of the weights are above and 18.1 per cent are below the probable limits of normal variation, instead of the expected 2.5 per cent. (It is to be noted that 17.4 per cent of the weights in latent cirrhosis in this age period were also found below the 2.5 percentile line.) It appears that in the earlier decades active cirrhosis may be accompanied by a hypertrophic or an atrophic liver, but that hypertrophy is to be expected rather than atrophy. This conclusion is supported by finding that such deviations in normal weights from the expected standard would not occur by chance once in a million times, since Chi-square is 215 and *P* is 0.000000. For the age period 50 to 89 years, the weights are 2.2 per cent above and 46 per cent below the probable limits of normal variation, where 2.5 per cent are expected normally. In other words, the normal number occur above the 97.5 percentile line, and a markedly disproportionate number fall below the 2.5 percentile line. Whereas a hypertrophic liver may be found in active cirrhosis in the later decades, atrophy is rather to be expected. Support for this statement is found in the fact that such deviations in normal weights from the expected standard would not occur by chance once in a million times, since Chi-square is 689.

The count of weights in active cirrhosis by quartiles for the total age period shows 24.8 per cent, or the normal number, in the upper quartile and a markedly disproportionate number, 51.8 per cent, in the lower quartile (table 5). This indicates that in active cirrhosis no more than the normal number of relatively large livers are to be found, but that relatively small livers are the rule. This is borne out by finding that this difference would not occur by chance alone once in a million times, since Chi-square is 57.9.

From the count of weights by quartiles for the age period from 20 to 49 years, it appears that a disproportionate number of weights are in the upper (50 per cent) and lower (34.0 per cent) quartiles (table 5). In this age period both more relatively large and more relatively small livers are found than would be expected from chance, since Chi-square is 23.6 and the larger weights predominate.

From the count of weights by quartiles for the age period from 50 to 89 years it is indicated that a disproportionately small number, 12.3 per

cent, are in the upper and a disproportionately large number, 60.6 per cent, are in the lower quartile, i. e., less than the normal number of relatively large livers and more than the normal number of relatively small livers (table 5). Whereas relatively large livers may sometimes be found after the age of 50 years, relatively small livers are the rule.

A disproportionate number, 61.6 per cent, of the weights of active cirrhotic livers are below the median line (table 5). In other words, in active cirrhosis the weights in approximately three fifths of the cases fall below the median line. Small livers rather than large are the rule in active cirrhosis. In the early decades, before 50 years, 61.3 per cent are above the median line, which could occur by chance 10 times in a hundred. In the later decades, after 50 years, 73 per cent are below the median line, which could not occur by chance once in a million times.

From these various analyses it appears that in the earlier decades active cirrhosis tends to be accompanied by hypertrophy of the liver and that in the later decades it is unquestionably accompanied by atrophy. Herein may lie the explanation of the origin of the terms hypertrophic cirrhosis and atrophic cirrhosis; in the young, hypertrophy is to be expected, and in the old, atrophy. Rolleston and McNee [4d] found the same tendency toward atrophy with advancing age, but apparently failed to recognize that the enlargement in latent cases might be due to differences in age.

In figures 2 and 3 the degree of microscopic change in each liver is shown by an appropriate mark. Inspection of these graphs indicates that in any degree of cirrhosis, whether active or latent, the liver may be large or small. It also appears that large or small cirrhotic livers may be accompanied by a slight or a pronounced degree of microscopic change. A comparison of the weights of the livers in latent and active cirrhosis, according to the degree of microscopic change, is shown in table 6. In this table it may be seen that in all degrees of cirrhosis, whether latent or active, disproportionate numbers are found above the 97.5 percentile line and below the 2.5 percentile line. In latent cirrhosis the various degrees of microscopic change are more or less equally represented by hypertrophy and atrophy, but in active cirrhosis the tendency toward atrophy is more definite. A comparison of latent and active cirrhosis in each degree of microscopic change shows that in grade 1 cirrhosis the difference could occur by chance 28 times in a hundred, since Chi-square is 5.5 and P is 0.28; hence no significant difference is demonstrable (Dunn [12]). However, in grade 2 cirrhosis the difference could occur only 17 times in a thousand, since Chi-square is 12.3 and P is 0.017, and so it is significant. Similarly, in grade 3 cirrhosis

12. Dunn, H. L.: Physiol. Rev. **9**:275, 1929.

the difference could occur by chance only 4 times in a hundred, since Chi-square is 10.3 and P is 0.04, and is significant.

Considering all livers below the 2.5 percentile line as atrophic, a comparison was made between the proportion of these livers occurring in latent and active cirrhosis according to the degree of cirrhosis and the group as a whole (table 7). Since the difference between the proportion of atrophic livers with grade 1 cirrhosis in the latent and active

TABLE 6.—*Comparison of the Incidence of the Weights of the Livers in Latent and Active Cirrhosis According to the Degree of Cirrhosis, Plotted on the Normal Standard*

	Number of Weights (Both Sexes)	Percentages of Weights Between Percentile Lines: Above 97.5 Line	97.5 to 75	75 to 25	25 to 2.5	Below 2.5 Line	n′	χ^2	P	Percentage of Weights: Above 50 Line	Below 50 Line
Percentage of weights expected	..	2.5	22.5	50	22.5	2.5	..	....	.....	50	50
Grade 1	45										
Latent type	29	10.3	0	58.6	13.7	17.2	5	5.5	0.28	34.4	65.5
Active type	16	12.5	12.5	21.2	18.7	25.0				43.7	56.2
Grade 2	57										
Latent type	28	10.7	39.2	24.9	14.2	10.7	5	12.3	0.017	64.2	35.7
Active type	29	13.7	13.7	13.7	10.3	48.2				34.4	65.5
Grade 3	104										
Latent type	16	25.0	37.5	18.7	6.2	12.5	5	10.3	0.040	68.7	31.2
Active type	88	11.3	12.5	24.9	15.9	35.2				38.6	61.3

TABLE 7.—*Percentage of Atrophic Livers According to Degree of Cirrhosis in Latent and Active Types*

	Latent Cases, Percentage	Active Cases, Percentage	Difference	R	P
Grade 1	17.24 ± 7.01	25.0 ± 10.8	7.76 ± 12.80	0.6	0.55
Grade 2	10.71 ± 5.86	48.27 ± 9.33	37.56 ± 10.96	3.42	0.00067
Grade 3	12.5 ± 8.26	35.22 ± 5.09	22.72 ± 9.71	2.33	0.016
All grades	13.69 ± 4.02	36.84 ± 4.18	23.15 ± 5.803	3.98	0.000063

groups is only 0.6 times its standard error, the difference is not significant. But the differences between the proportion in latent and active grade 2 cirrhosis, in latent and active grade 3 cirrhosis and in latent and active cirrhosis as a whole are significant, since they are 3.4, 2.3 and 3.9 times their standard errors, respectively; i. e., they would occur by chance alone 67 times in a hundred thousand, 16 times in a thousand and 6 times in a hundred thousand, respectively. If a large enough series of cases of cirrhosis with grade 1 microscopic change were available, it is possible that a difference might be demonstrable between the latent and active types in which the livers were atrophic, but this is not

likely. There is a demonstrable difference in the incidence of atrophy of the liver in the latent and active types when more marked microscopic changes are present. The same is true when the severity of the process is disregarded and the two types are compared.

These analyses suggest that the size of the liver and the degree of microscopic change are not responsible for the clinical signs of activity, but that the activity of the cirrhotic process is responsible for the size of the liver and the degree of microscopic change.

Since hemorrhage may exert an influence on the weight of the liver, the patients who died of active cirrhosis and who had hemorrhage are

TABLE 8.—*Comparison of the Weights of Spleens in Cirrhosis with Normal Averages According to Sex, Age and Maximum, Minimum and Average Weights*

	Males					Females				
Decades	Number of Cases	Maximum Weight	Minimum Weight	Average Weight	Boyd's Normal Average	Number of Cases	Maximum Weight	Minimum Weight	Average Weight	Boyd's Normal Average
				Latent Cases						
20-29	3	570	180	313	204	..	...	...	...	168
30-39	5	800	154	352	168	..	...	...	...	164
40-49	10	670	57	259	179	2	500	255	377	172
50-59	17	463	70	227	127	3	600	300	400	133
60-69	17	462	75	211	132	3	425	270	332	129
70-79	9	400	85	205	123	..	...	...	...	121
80-89	2	450	100	275	...	1	...	77	77	81
Average				236					320	
				Active Cases						
20-29	2	510	335	423	204	2	300	250	275	168
30-39	12	925	110	483	168	5	590	190	384	164
40-49	16	1,085	50	397	179	7	470	125	263	172
50-59	28	2,060	70	412	127	8	980	160	419	133
60-69	23	875	92	356	132	9	600	140	299	129
70-79	13	855	70	282	123	5	300	100	199	121
80-89	..	...	...	...	...	..	...	...	...	81
Average				391					317	

indicated by a dash from the respective marks (fig. 3). From inspection of this graph, hemorrhage does not appear to be an important factor in the decrease in the weight of the liver in the active cases of cirrhosis in this series. As Boyd found that in normal persons who died of acute hemorrhage the livers weighed significantly less than in normal persons who died as a result of accidents without hemorrhage, a comparison was made between the weights of the livers in active cirrhosis with and without hemorrhage. No significant difference could be demonstrated.

OBSERVATIONS ON THE WEIGHT OF THE SPLEEN

A somewhat similar study was made of the weights of the spleens in this series of cases of cirrhosis of the liver, but no microscopic examination of the spleens was made.

Table 8 shows a comparison of the weights of the spleens with the normal averages obtained by Boyd. From this table it appears that while there is a great variation in weights, nevertheless, in both latent and active cirrhosis, especially in the latter, the spleen tends to be enlarged. Normally the spleen decreases in weight with advancing age, but there is no definite evidence of any such tendency when active cirrhosis of the liver is present. There is a reduction in the averages in the male with advancing age, but the average is still much higher

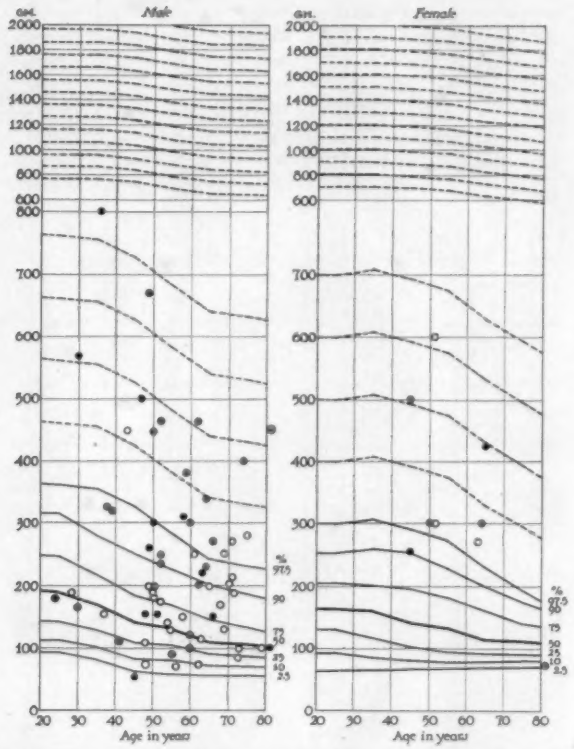

Fig. 4.—Dispersion of the weights of the spleens in the cases of latent cirrhosis of the liver plotted on the standard of normal variability in weight.

than the normal average for the corresponding decades. It is to be noted that quite small spleens may be found in both latent and active cases of cirrhosis of the liver.

To carry the analysis further, the weights of the spleens were plotted on the standard of normal variability in weight of the spleen constructed by Boyd (figs. 4 and 5). The number of weights found in each of the eight zones is shown in percentages in table 9. In these graphs the tendency to enlargement of the spleen, whether the cirrhosis of the liver is latent or active, is obvious. Although some

patients with cirrhosis of the liver have very small spleens, as a rule a person with active cirrhosis has a larger spleen than a person with latent cirrhosis.

In table 9 in each instance the disproportionately large numbers of weights above the 97.5 percentile line, the 75 percentile line and the 50 percentile line are obvious. In each instance this disproportion is more marked in active than in latent cirrhosis. The disproportionately

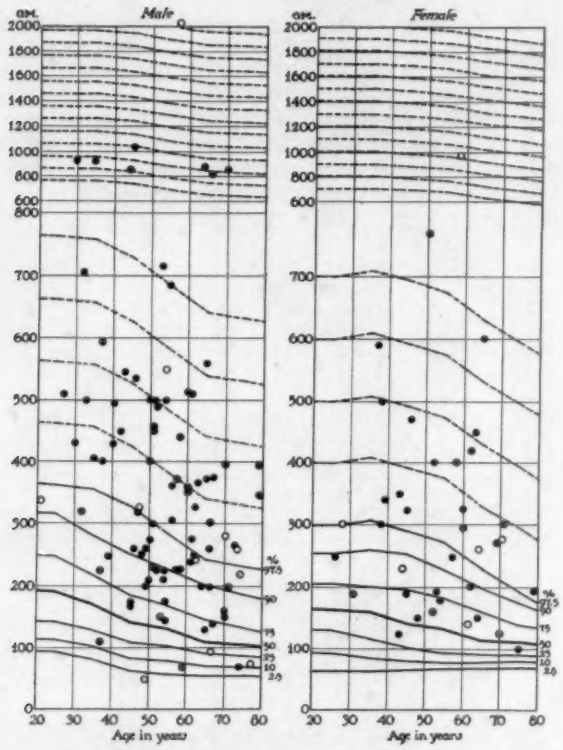

Fig. 5.—Dispersion of the weights of the spleens in the cases of active cirrhosis of the liver, plotted on the standard of normal variability in weight.

small number of weights below the 2.5 percentile line, the 25 percentile line and the 50 percentile line is also very striking. It may be seen that, regardless of how the weights of the spleens in active and latent cirrhosis of the liver are grouped, with but 1 exception the chances that the differences found were due to sampling alone are less than 1 in a million. In all cases the differences are significant. The almost constant enlargement of the spleen in cirrhosis of the liver, whether active or latent, makes one wonder which organ is involved first by the process.

TABLE 9.—*Comparison of the Weights of the Spleens in Cirrhosis of the Liver with the Normal Standard* *

	Number of Weights (Both Sexes)	Percentage of Weights Between Percentile Lines								n′	χ^2	P	Percentage of Weights	
		Above 97.5 Line	97.5 to 90	90 to 75	75 to 50	50 to 25	25 to 10	10 to 2.5	Below 2.5 Line				Above 50 Line	Below 50 Line
Percentage of weights expected.....	..	2.5	7.5	15	25	25	15	7.5	2.5	..	.....	.....	50	50
Latent cirrhosis	72	34.7	16.6	13.8	12.5	11.1	5.5	4.1	1.3	8	322.6	0.000000	77.7	22.2
20-49 years	20	30.0	20.0	5.0	10.0	20.0	5.0	5.0	5.0	8	69.9	0.000000	65.0	35.0
50-89 years	52	36.5	15.3	17.3	13.5	7.6	5.6	3.8	0.0	8	161.3	0.000000	82.6	17.3
Active cirrhosis	130	59.2	11.5	12.3	10.7	2.3	2.3	0.7	0.7	8	1,737.7	0.000000	93.8	6.1
20-49 years	44	59.0	11.3	11.3	11.3	2.2	2.2	0.0	2.2	8	585.3	0.000000	93.1	6.8
50-89 years	86	59.3	11.6	12.7	10.4	2.3	2.3	1.1	0.0	8	1,153.0	0.000000	94.1	5.8
		Above 75 Line			75 to 50	50 to 25		Below 25 Line						
Percentage of weights expected.....	..	25			25	25		25						
Latent cirrhosis	72	65.2			12.5	11.1		11.1		4	62.3	0.000000	77.7	22.2
20-49 years	20	55.0			10.0	20.0		15.0		4	10.0	0.018	65.0	35.0
50-89 years	52	69.2			13.5	7.6		9.6		4	61.9	0.000000	82.6	17.3
Active cirrhosis	130	83.0			10.7	2.3		3.8		4	235.9	0.000000	93.8	6.1
20-49 years	44	81.8			11.3	2.2		4.5		4	76.5	0.000000	93.1	6.8
50-89 years	86	83.7			10.4	2.3		3.4		4	159.4	0.000000	94.1	5.8
		Above 50 Line				Below 50 Line								
Percentage of weights expected.....	..	50				50								
Latent cirrhosis	72	77.8				22.2				2	22.2	0.000000	77.7	22.2
Active cirrhosis	130	93.8				6.1				2	103.0	0.000000	93.8	6.1

* Sex has been eliminated in this table, since the cases found in the corresponding zones may be added without introducing an error.

A comparison has been made of the weights of the spleens according to the degree of cirrhosis which was present in the livers (table 10). It appears that in both latent and active cirrhosis high degrees of microscopic change in the liver tend to be accompanied by a larger spleen than is the case with slighter changes in the liver, and, further, that the spleen tends to be larger in active than in latent cirrhosis. A comparison of the weights of the spleens in corresponding degrees

TABLE 10.—*Comparison of the Relation of the Weights of the Spleen in Cirrhosis of the Liver with the Normal Standard, According to the Degree of Cirrhosis of the Liver in the Latent and Active Types*

	Number of Weights (Both Sexes)	Percentage of Weights Between the Percentile Lines								Percentage of Weights	
		Above 97.5 Line	97.5 to 75	75 to 25	25 to 2.5	Below 2.5 Line	n′	χ^{2*}	P	Above 50 Line	Below 50 Line
Percentage of weights expected	..	2.5	22.5	50	22.5	2.5	..	...	....	50	50
Grade 1 cirrhosis	47										
Latent type	30	23.3	33.3	29.9	13.3	0	5	7.0	0.13	73.2	26.5
Active type	17	52.9	23.4	11.6	5.8	5.8				82.3	17.6
Grade 2 cirrhosis	55										
Latent type	28	46.4	24.9	17.7	10.6	0	5	1.6	0.8	74.9	24.8
Active type	27	62.9	14.8	14.8	7.4	0				92.5	7.4
Grade 3 cirrhosis	100										
Latent type	14	35.7	35.6	21.4	0	7.1	5	7.2	0.13	92.7	7.1
Active type	86	59.3	26.7	12.7	1.1	0				96.4	3.4

* Determined by the Chi-square technic for comparing two observed distributions (Dunn).

TABLE 11.—*Percentage of Hypertrophied Spleens According to the Degree of Cirrhosis of the Liver in the Latent and Active Types*

	Latent Type, Percentage	Active Type, Percentage	Difference	R	P
Grade 1	23.33 ± 7.72	52.94 ± 12.11	29.61 ± 14.35	2.06	0.04
Grade 2	46.42 ± 9.04	62.96 ± 9.29	16.54 ± 13.23	1.25	0.211
Grade 3	35.71 ± 12.81	59.3 ± 5.29	23.59 ± 13.85	1.70	0.089
All grades	34.72 ± 5.61	59.23 ± 5.19	24.51 ± 7.64	3.20	0.0014

of sclerotic change in the liver shows no demonstrable difference, since in the three degrees these differences could occur by chance as often as 13, 80 and 13 times in a hundred.

Considering all spleens above the 97.5 percentile line as hypertrophic, a comparison was made between the proportion of these spleens occurring in latent and active cirrhosis according to the degree of cirrhosis of the liver and the group as a whole (table 11). The difference between the proportions must be at least twice its standard error to be significant. It appears that there is a possibly significant difference

between latent and active grade 1 cirrhosis and that a significant difference is not demonstrable in grade 2 and grade 3 cirrhosis. However, when the degree of microscopic change in the liver is disregarded, there is a definitely significant difference in the weights of the hypertrophied spleens in latent and active cirrhosis, since the differences found could be due to sampling only 14 times in ten thousand. Comparison between the weights of the hypertrophied spleens by degree in each type of cirrhosis shows no demonstrable difference.

TABLE 12.—*Causes of Death in Hepatic Cirrhosis*

Latent Cases		Active Cases	
Heart disease	22	Cirrhosis	74
Accident	12	Hemorrhage	18
Peritonitis	5	Peritonitis	12
Pneumonia	5	Peritonitis (tuberculous)	2
Pulmonary tuberculosis	4	Heart disease	6
Cerebral hemorrhage	4	Pneumonia	5
Meningitis	3	Accident	4
Diabetes mellitus	3	Carcinoma (stomach)	3
Carcinoma (stomach)	3	Cerebral hemorrhage	3
Alcoholism	3	Strangulated hernia	2
Carcinoma (colon)	3	Carcinoma (liver)	2
Wilson's disease	2	Pulmonary abscess	2
Pericarditis	2	Sepsis	2
Encephalomalacia	2	Alcoholism	2
Gunshot wounds	2	Enteritis	2
Carbon monoxide poisoning	2	Postoperative shock	2
Suppurative pancreatitis	1	Miliary tuberculosis	1
Suppurative cholecystitis	1	Chronic nephritis	1
Pulmonary abscess	1	Syphilis	1
Syphilis	1	Postoperative hemorrhage	1
Empyema	1	Diphtheria	1
Strangulated hernia	1	Carcinoma (colon)	1
Carcinoma (prostate)	1	Burn	1
Pulmonary embolism	1	Carcinoma (hepatic duct)	1
Heat stroke	1	Carcinoma (prostate)	1
Carcinoma (cervix)	1	Mesenteric thrombosis	1
		Pernicious anemia	1
		Pericarditis	1
		Purpura	1
		Erysipelas	1
		Hodgkin's disease	1
		Starvation	1
		Sudden death	1

CAUSES OF DEATH

Table 12 sets forth the causes of death in the two groups and shows that a great variety of conditions were responsible for death. Heart disease was the major cause of death in the cases in the latent group, but was the cause of death in but a comparatively small number of the cases of active cirrhosis. The 5 cases of peritonitis in the latent series resulted from carcinoma of the gastro-intestinal tract in 3 cases, pelvic abscess in 1 case and duodenal ulcer in 1 case. Attention should be called to the low incidence of tuberculous peritonitis (2 cases), since the statement has been made that it occurs in 10 per cent of all cases of cirrhosis. In this series its incidence is less than 1 per cent.

CONCLUSIONS

Two hundred and forty-five cases of portal cirrhosis found in routine postmortem examinations of the bodies of 11,912 adults are reported. This is an incidence of 2.05 per cent. No patient for whom an exact age was given was over 89 years of age, and only 1 patient in the active group was over 80 years of age.

Of these cases, 64.4 per cent are considered as active and 35.5 per cent as latent.

The corrected ratio of males to females in the latent group is 3.5 : 1, and in the active group, 1.1 : 1. This shows practically no difference in the sex incidence of the disease in patients who had had symptoms of cirrhosis. It bears out the statements of Yeld and of Rolleston and McNee that cirrhosis is latent more often in males.

The distribution of active and latent cirrhosis according to decades of life is practically identical; approximately 70 per cent of the cases occurred in persons between the ages of 40 and 69 years.

Persons with latent cirrhosis tend to have a less advanced cirrhotic process than is found in the active group.

In cirrhosis the dispersion of the weights of the livers is increased both above and below normal limits. This is more marked in active than in latent cirrhosis. In active cirrhosis there are a disproportionately large number of hypertrophic livers in the earlier decades of adult life and a disproportionately large number of atrophic livers in the later decades.

Livers which show the more advanced degrees of cirrhosis tend to be smaller than those in which the process is less advanced. This is particularly true of those which have given rise to symptoms.

Hemorrhage as a cause of the decreased weight is apparently unimportant.

The spleen is usually markedly enlarged in cirrhosis of the liver, and the enlargement is more frequent in the active than in the latent cases.

Heart disease is the most frequent cause of death in latent cirrhosis, but is a relatively infrequent cause in active cirrhosis.

EFFECT OF ROENTGEN IRRADIATION ON THE HEALING OF WOUNDS

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In conducting an investigation on the effect of roentgen rays on the healing of wounds, Dr. E. A. Pohle and I obtained certain striking results. These have been reported in the radiologic literature,[1] but the pathologic observations are deemed of sufficient interest for publication in more detail.

METHODS

White rats of the same strain and of approximately uniform size were used. These animals were chosen as they were available in large numbers and easily cared for. A single dose of 1,000 roentgens was given in each instance. In the first set of these experiments,[1a] it was found that results did not vary with the quality of radiation; accordingly, the following type of irradiation was used in the experiments to be discussed here: 100 kilovolts, 2 mm. aluminum, 20 cm. focal skin distance, effective 0.34 angstrom (transmitted through 2 mm. aluminum, 0.7 roentgen per second).

Seventy-eight animals were used, and in each a wound approximately 6 cm. long was made in the skin of the back, one Michel clip being applied to prevent excessive gaping. Metaphen was used as a disinfectant. One half of each wound was treated, the other half being left as a control. Irradiation was done in one group immediately, in another twenty-four hours after incision, and in a third, forty-eight hours after incision, the rats falling into three general groups according to the interval between cutting and exposure. The progress of healing was traced by daily stages, rats in each general group being killed from one to nine days after incision. The tissues were fixed in a trinitrophenol formaldehyde solution,[2] embedded in paraffin and stained with hematoxylin and eosin and with hematoxylin and van Gieson's stain. Twelve of the seventy-eight animals were discarded on account of infection of the wounds, so that this report is in reality based on the results found in sixty-six animals.

RESULTS

In the reporting of results, the animals naturally fall into the three general groups indicated. Since the effect of irradiation was in principle the same in all groups and differed in different animals only in degree, this effect will be discussed first in general, and quantitative considerations will be taken up later.

From the departments of pathology and radiology, University of Wisconsin.

1. (*a*) Pohle, E. A.; Ritchie, G., and Wright, C. S.: Radiology **16**:445, 1931. (*b*) Pohle, E. A., and Ritchie, G.: ibid. **20**:102, 1933.

2. Bouin's solution is composed of the following: solution of formaldehyde, U. S. P., 500 cc.; distilled water, 1,500 cc.; glacial acetic acid, 100 cc.; trinitrophenol to saturation point.

Three chief effects were noted: (1) retardation of fibroblastic growth; (2) a change in the fibroblastic development, with the production of abnormal cells, and (3) the formation of a fibrin network, poor in cells, which persisted in many cases beyond the usual time for such an exudate.

1. The first of these, the retardation of growth, was the most striking and the most important phenomenon to be seen. It was present to a great degree in some animals, in which the irradiated portion of the wound showed absolutely barren margins with apparently no attempt at healing, while in the control portion complete closure by an abundant fibroblastic growth supervened (fig. 1). Apparently the scavenger

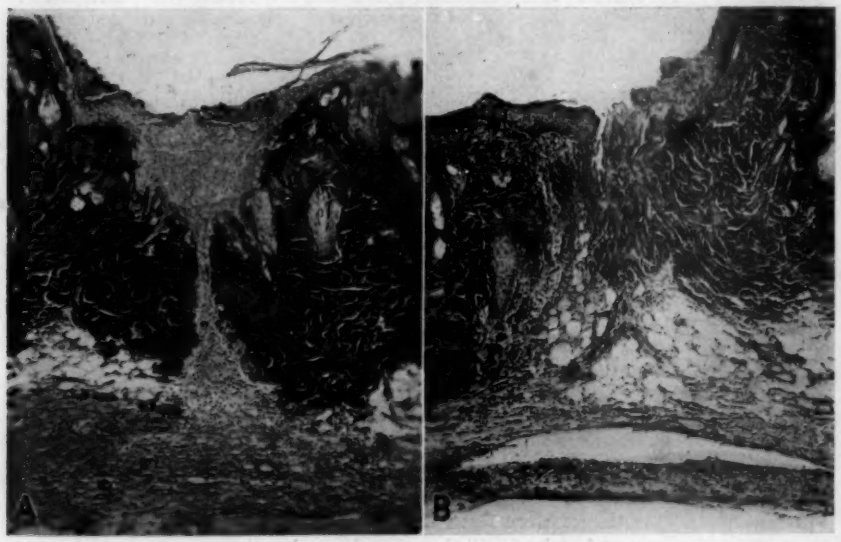

Fig. 1 (rat 10).—Photomicrographs of tissue taken from a wound treated twenty-four hours after cutting; the sections were taken eight days after cutting. *A* shows the treated part; *B*, the untreated part. Note the inflammatory exudate and lack of fibroblastic growth in *A*, and the inconspicuous scar in *B*. Hematoxylin and van Gieson stain. Zeiss apochr. 5, homal II; × 50.

mechanism was not impaired in many cases, for the phagocytic cells seem to have cleared up the traumatic inflammatory exudate entirely, leaving the two edges of the cut close together, but separated by a histologic open space (fig. 2).

2. The atypical cells seen were in the form of fibroblastic giant cells. The chief difference from typical fibroblasts was in the size of the cells. There was usually no great distortion or abnormality of shape noted; the nuclei, though abnormally large, maintained for the most part the usual oval shape, though the nucleoli were more accentuated than in

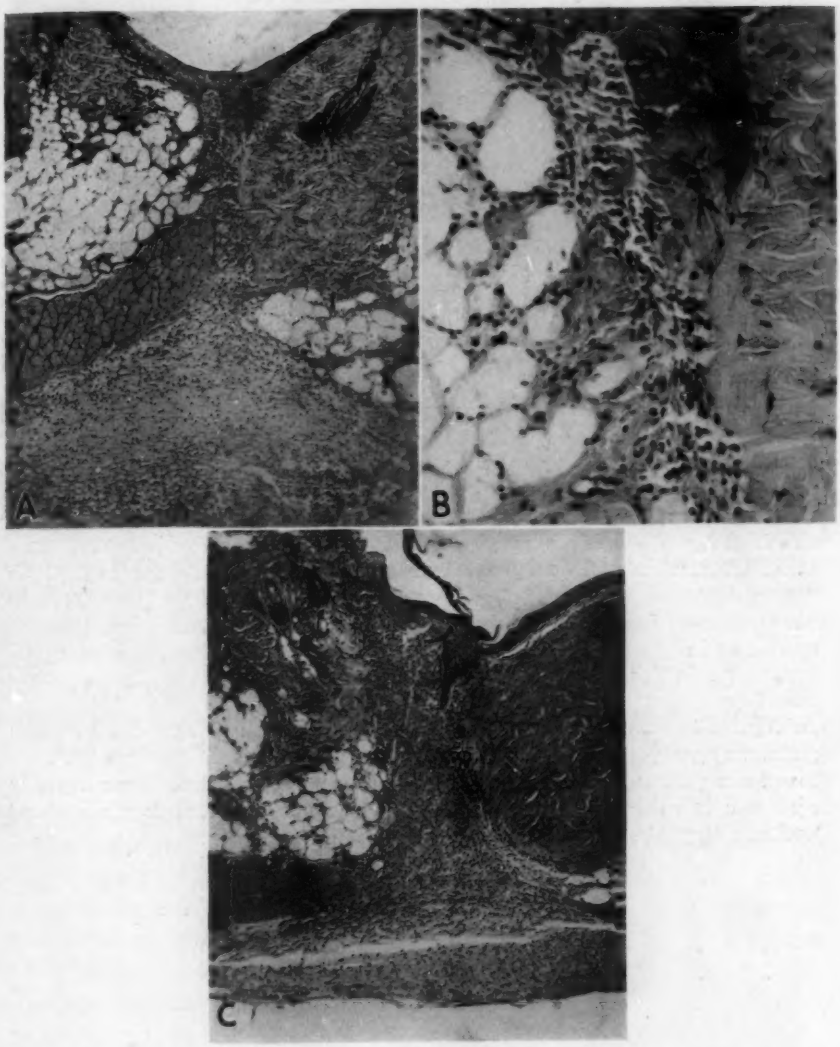

Fig. 2 (rat 3).—Photomicrographs of tissue from a wound irradiated immediately after cutting; the sections were taken seven days after cutting. *A* shows the treated part; *B*, detail of *A*; *C*, the untreated part. There is good approximation in *A*, with complete epithelial repair, but lack of fibroblastic growth, leaving a histologic space; also abundant unorganized inflammatory exudate in the deeper portion. Hematoxylin and eosin. *A* and *C*, Zeiss apochr. 5, homal II (× 50); *B*, Zeiss apochr. 10, homal I; × 175.

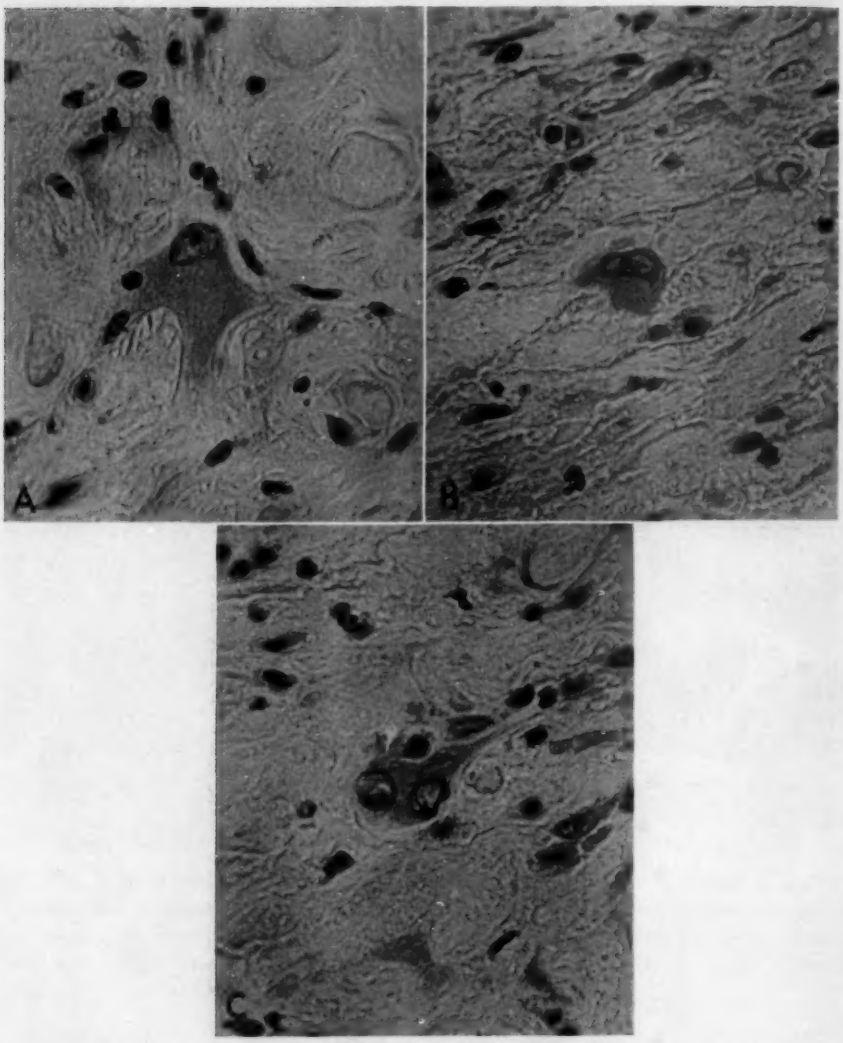

Fig. 3 (rat 16).—Photomicrographs of tissue from a wound exposed to irradiation forty-eight hours after incision. The sections were taken eight days after incision. In *A* a fibroblastic giant cell is seen in the treated part of the wound. In the surrounding tissues are inflammatory and connective tissue cells of usual size. In *B* is seen a fibroblastic giant cell with an indented nucleus; in *C*, a giant fibroblast with two nuclei. Iron hematoxylin stain. Zeiss apochr. 20, homal I; × 470.

the control specimens (fig. 3 *A*); occasionally a nucleus was considerably indented (fig. 3 *B*), or there were two nuclei in one cell (fig. 3 *C*). This qualitative change in the repair process was the most frequent one seen, and was present even in several instances in which healing seemed as far advanced in the exposed part as in the control part of the wound.

3. The loose fibrin network seen in several cases was undoubtedly the remains of the original traumatic inflammatory exudate brought out by the injury to the tissue in cutting. It was noted formerly in our work, and its presence probably arose from a lack of proteolytic activity on the part of the cells in the region of the wound. This network was refractile, stained pink with eosin and yellow with van Gieson's stain, and seemed to be identical in all respects with that described by Maximow in his work with irradiated inflammatory tissue.

A quantitative analysis of these observations is of considerable interest. For convenience, the aforementioned groups of animals will be known as the "immediate," the twenty-four hour and the forty-eight hour group.

In the immediate group (total, twenty-nine animals), healing in the irradiated portions was retarded in thirteen. This delay was first noticeable three days after incision, and was present in all four animals killed six days after cutting. The examination of four seven day old wounds revealed delayed healing in the irradiated portions of two.

In the twenty-four hour group, the largest proportion of wounds with retarded healing resulted. Of twenty animals in this group, thirteen showed delayed healing in the treated parts. This retardation was first evident four days after incision, and was a constant observation at from five days to eight days, the extent of the experiment in this group.

In the forty-eight hour group, only five of seventeen animals showed positive results. In the rest there was no retardation of healing. No stage was found in the incisions at which a delay in healing was constant.

To sum up this portion of the results, delayed healing was present in thirty-one of sixty-six animals; the x-rays seemed most deleterious when administered twenty-four hours after incision, less so when roentgen treatment was applied immediately, and least deleterious in the forty-eight hour group. It may be said that in tabulating these results, only those differences which were absolutely clearcut were accepted as positive. In three animals a reversal of the usual effect was found; that is, there was an advance in healing in the treated portions over that found in the control parts. I am somewhat at a loss to explain this; since it occurred in such a small proportion of the total number of animals, I have laid it to technical error, a conclusion which I feel is fairly justified.

As mentioned previously, the formation of fibroblastic giant cells was the most frequent change noted. In forty-one of the sixty-six animals, these abnormal cells were found, being present in almost all cases in which a definite difference in healing could be detected between treated and untreated parts, and in several in which no such difference was noted. These cells appeared as early as two days after cutting (in two animals of the immediate group) and were present as late as nine days after cutting. Slight irregularities of fibroblasts were seen in some control tissues, but in no case were they as definite and striking as in the experimental portions. They were found in thirteen of the immediate group (total, twenty-nine), fifteen of the twenty-four hour group (total, twenty), and thirteen of the forty-eight hour group (total, seventeen). These proportions would seem to place this change as the most frequent and characteristic response to roentgen irradiation, though not the most important from a practical point of view, as it does not seem to affect the progress of healing.

The presence of a fibrin network is perhaps more difficult to evaluate quantitatively. In a wound which is not completely closed by sutures or clips, one would expect to find in all cases a certain amount of fibrinous exudate, usually more abundant in some parts of the wound than in others; the decision as to whether this is excessive must of necessity be arbitrary. For this reason I consider this phenomenon the least important of the three under discussion. For the sake of completeness, however, it might be well to make a brief statement as to quantitative results. I have eliminated for this purpose all animals killed four days or less after cutting, since a fairly large amount of fibrin network is certain to be present up to this time and even later. The phenomenon increases in significance, I believe, with an increase in the time after incision; under ordinary circumstances none should be present at seven days. Taking these facts into consideration, the network was present in only a small proportion of the animals: only fourteen of the sixty-six—four in the immediate group, seven in the twenty-four hour group and three in the forty-eight hour group.

The proportion of positive results previously mentioned may seem low until one considers that for the sake of completeness observations were begun in all three groups before any marked changes had taken place, and these early observations add to the proportion of negative results.

Here it may be noted also that in several instances the regenerated epithelium had completely covered the wound, while the underlying connective tissue showed no growth. The importance of this will be taken up later.

COMMENT

This subject may be regarded from two points of view: the first consideration is the treatment of the wounds, either with the purpose of acceleration of healing or with that of obtaining a better cosmetic effect; the second consideration is the postoperative irradiation of malignant tumors. Since the latter is by far the more important, attention has been devoted in this investigation entirely to that phase of the problem. For this reason the constant dose of 1,000 roentgens was chosen as approximating an average therapeutic dose. This appears high, but one must remember that when a dose of 500 roentgens is applied over a fairly large area, as in the treatment of carcinoma, the actual dose delivered, owing to back-scattering, may be as high as 700 roentgens. On the other hand, with the small areas used here (usually 1 by 3 cm.), the back-scattering is negligible, and the measured dose is for all practical purposes identical with the dose delivered to the tissues. Our dose is a little over the average one given in one sitting in the treatment of malignant new growths.

The results obtained here are practically identical with those of Maximow,[3] who induced inflammation by the introduction of blocks of sterile pyroxylin (celloidin) under the skin. He administered about 12 Kienböck units at a sitting, with daily sittings ranging in number from one to fifteen. His paper does not give all the factors, but from those given I have calculated that the daily dosage was probably about 450 roentgens, given over a circular area 4 cm. in diameter. He found excessive fibrin, malformed fibroblasts and a lack of ability to form collagenous tissue in all cases, the changes differing only in degree according to the number of exposures. He found also that after complete healing the scars in experimental tissues were identical with control scars.

The mechanism of the delayed healing and of the formation of fibroblastic giant cells seems fairly clear in the light of modern radiobiology. It is generally agreed from work with tissue culture that cells in a process of mitotic division are most susceptible to the influence of x-rays; this is borne out by clinical and experimental observations. It is therefore natural that the fibroblasts, being in a most active state of proliferation, should show striking anomalies under the influence of an agent designed expressly to damage rapidly reproducing cells. One might expect to find a similar effect on the endothelium of the newly formed blood vessels, but such is not the case: A diligent search revealed only a normal capillary lining, without giant cells. The reason for this is not certain, but should probably be attributed to that obscure phenomenon, the biologic difference in susceptibility of different tissues to physical and chemical agents.

3. Maximow, A. A.: J. Exper. Med. **37**:319, 1923.

The relation of this anomalous fibroblastic formation to the rate of healing is not quite clear. It occurred in greatest proportion in the forty-eight hour group, in which the delayed healing was least frequent; it could therefore perhaps be regarded as evidence of slight cellular injury, as opposed to a more severe injury resulting in lack of regenerative activity and consequent sluggish healing.

The persistence of the fibrin network is also difficult to explain. Observation in general points toward the digestion of a fibrinous inflammatory exudate by the incoming phagocytic cells, though it sometimes takes place when relatively few of these are present. It is rather hard to conceive of an impairment of the function of incoming cells by localized irradiation lasting a comparatively short time (twenty-five minutes). The two most probable reasons for persistence of the fibrin network are, first, a change in the local p_H, caused by a perverted metabolism of the cells affected by roentgen rays, and, second, the lack of an enzyme supposedly secreted by the fibroblasts. Conclusive evidence in favor of either of these suppositions is lacking, so far as I have been able to ascertain. Von Gaza [4] stated that during the healing process the newly formed fibroblasts and capillary endothelial cells take a phagocytic part in the clearing up of débris, but he cited no experimental evidence as a basis for his statement. It is a well known fact, however, that in tissue cultures of fibroblasts, the culture medium becomes softened and digested in a short time. Santesson [5] reported a definite decrease in this softening following irradiation of cultures of chicken sarcoma. This would seem to indicate that there is a proteolytic enzyme secreted by such cells in culture, and further that this secretion is reduced by roentgen irradiation. The fact that x-rays, although causing destruction of cells, decrease the digestion of the medium, would lead one further to believe that this enzyme is not merely set free by the breaking down of dead cells, but is actually secreted by the living cells. It is recognized, of course, that such fragmentary evidence drawn from experiments with tissue cultures cannot be the basis of closely knit deduction applied to tissues in vivo; the facts are merely presented as being suggestive.

The question as to why the tissues appear most susceptible about twenty-four hours after injury is also a matter for considerable conjecture. Careful microscopic examination of our wound material does not lead to a satisfactory answer, but on the contrary merely convinces me that the problem is essentially a biologic one, not to be solved with present day histologic technic. A cursory review of the literature con-

4. von Gaza, W., in Bethe, A.; von Bergmann, G.; Embden, G., and Ellinger, A.: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1926, vol. 14, pt. 1, p. 1152.

5. Santesson, L.: Upsala läkaref. förh. **34**:591, 1928; abstr., Zentralbl. f. d. ges. Radiol. **6**:252, 1929.

cerning tissue cultures as influenced by irradiation, however, leads one to two definite conclusions: (1) A cell in, or about to undergo, mitosis is especially sensitive to the influence of roentgen rays; (2) therefore, the stage at which a tissue is most actively growing (hence contains the most mitotic figures) is the stage at which that tissue will be most susceptible. Opinions have varied as to the exact time when a cell is most sensitive. Markovits [6] advanced the opinion that a cell in the equatorial plate stage is most easily destroyed. Love,[7] in a series of experiments in which he used cultures of cells from the choroid and sclerotic of chick embryos, calculated that when a cell was within three hours of dividing (that is, when it was destined to divide at any time within the next three hours) its sensitivity to x-rays was constant; when such a period was over three hours, the sensitivity decreased. He believes that the reduction of mitoses in a culture exposed to roentgen rays is caused by an inhibition of the cells falling within the three hour stage.

Again we have evidence from experiments with tissue cultures which cannot be taken bodily and applied to naturally growing tissues. Still, when we link these facts to our knowledge in regard to malignant tumors and their susceptibility to x-rays, I think that we may safely deduce from the results obtained that the stage of most rapid cell growth in the healing of the experimental wounds occurred at a time not far from twenty-four hours after the wounds were made.

Another parallel may be drawn between experiments with tissue cultures and results obtained in the tissues themselves. When cells in tissue cultures are exposed to a dose of x-rays which injures the cells but does not cause actual death of the culture, the ultimate result is in most cases complete recovery, and after several days experimental and control cultures cannot be differentiated microscopically. Maximow [8] found that scars in irradiated inflammatory tissue were identical with those in control inflammatory tissues, although, as previously related, x-rays exerted a striking influence on the earlier changes. Again, Pohle, Wright and I,[1a] working with rats, noted that although a single dose of 1,000 roentgens definitely delayed healing, the ultimate result was identical with that seen in unirradiated wounds, both grossly and microscopically.

A survey of the literature dealing specifically with the effect of roentgen irradiation on the healing of wounds reveals a surprising lack of attention to this important subject; indeed, no accurately controlled experimental work applying modern dosimetry has been reported, to my knowledge.

6. Markovits, J.: Arch. f. exper. Zellforsch. **6**:315, 1928.
7. Love, W. H.: Arch. f. exper. Zellforsch. **11**:435, 1931.

Haberland,[8] in 1923, irradiated Thiersch skin grafts in nine dogs, and found a delay in healing. The difference between the control and experimental grafts was found to have disappeared after ten days. The dose used is given as from one-third to two-thirds unit skin dose, but since no qualifying data are given, it is impossible to calculate this accurately in roentgens. The highest dose was probably, however, not more than 400 roentgens. No histologic observations are given.

In 1928, Frey [9] undertook a series of experiments designed to ascertain the vascular reaction to exposure to roentgen rays. He drew certain conclusions as to the healing of wounds after irradiation which I feel are not valid, as he did not work with wounds, reported no histologic observations and assumed that the reaction of the tissues was entirely vascular.

In the same year, Cazzamali [10] injected trypan blue into the tissues a few days before and immediately following the production of wounds. He concluded that exposure to x-rays caused an earlier mobilization of the reticulo-endothelial elements in the healing process. The original article was not available to me, and the details of method and dosage are not given in the abstract.

Schürch and Tschudi [11] found that wounds treated with roentgen rays healed more quickly when they were made by means of electric cautery than with an ordinary scalpel. No histologic results were recorded.

F. Freund [12] and Fukase,[13] working together, applied 400 roentgens to freshly made wounds in the skin of rabbits and noted acceleration of healing, with a decrease in the inflammatory exudate, particularly in the leukocytes. Recent work by Buhtz [14] indicates, however, that Freund and Fukase did not begin their observations soon enough after incision; in the first few hours there is an increased outpouring of leukocytes, which disappear rapidly, giving the impression later of a decrease in exudate.

Businco and Cardia [15] used dogs, four in all, and made two wounds on the back of each. They used one wound for the experiment and the other, on the opposite side of the vertebral column, as a control. The dose was one-third erythema dose, spark gap 30 cm., filter 3 mm. aluminum (about 150 roentgens), given to two dogs at a single sitting,

8. Haberland, H. F. O.: Klin. Wchnschr. **2**:353, 1923.

9. Frey, S.: Beitr. z. klin. Chir. **144**:574, 1928; Deutsche Ztschr. f. Chir. **212**:324, 1928.

10. Cazzamali, P.: Abstr., Clin. chir. **4**:781, 1928.

11. Schürch, O., and Tschudi, E.: Strahlentherapie **32**:143, 1929.

12. Freund, F.: Strahlentherapie **33**:375, 1929.

13. Fukase, S.: Virchows Arch. f. path. Anat. **273**:794, 1929.

14. Buhtz, H.: Frankfurt. Ztschr. f. Path. **44**:57, 1932.

15. Businco, O., and Cardia, A.: Riv. di radiol. e fis. med. **2**:378, 1930.

twenty-four hours after cutting, and to the other two dogs in two sittings (after twelve hours and three days, and after twenty-four hours and four days). This resulted in a stimulation and acceleration of healing. Histologic results were promised for a later communication, but this I have not been able to find.

In a series of experiments on rabbits, Podestá [16] found that the irradiation of wounds, with either x-rays or radium, caused a delay in healing up to complete lack of closure, according to the dosage. His dose of roentgen rays varied "from a simple epilation dose to one causing a severe radiodermatitis, always with a heavy filter." There resulted necrosis in the depths of all wounds, and he concluded that if a heavy dose of either radium or x-rays is given over a fresh wound, necrotic tissue must be allowed to slough out before healing can be expected.

D'Istria and di Bello [17] carried out an investigation, using various sorts of radiation on wounds. Their method consisted in stripping the skin from measured areas on the backs of animals and noting the progress of healing by daily measuring the unhealed areas. They reported an acceleration of healing by the use of doses ranging from 0.625 to 10 Holzknecht units (from 63 to 1,000 roentgens). Especial interest attaches to the fact that in this range, the smaller the dose used, the greater was the acceleration obtained. No histologic results were reported.

Thus, in spite of somewhat conflicting evidence, it appears from the various experimental investigations available that a small dose stimulates the healing process, whereas a larger one, approximating those used in the treatment of malignant tumors, causes a delay.

Clinical notes on this subject are not uniform as to the conclusions drawn, but in general bear out the experimental evidence. Vogt,[18] in 1922, stated that preoperative irradiation caused no impairment of cicatrization. This is in accord with the observations of Pohle, Wright and myself.

In 1924, Schück [19] reported briefly a series of cases in which he had treated various inflammatory conditions, such as pneumonia, with roentgen rays, with some apparent success. Heidenhain and Fried,[20] in the same year, reported a rather similar series of cases, with like results. No dosage is given in either communication. Halberstaedter and Simons (1926) [21] stated that in their experience roentgen irradia-

16. Podestá, V.: Riv. di radiol. e fis. med. **2**:446, 1930.
17. d'Istria, A., and di Bello, F.: Actinoterapia **9**:95, 1930.
18. Vogt, E.: Med. Klin. **18**:1491, 1922.
19. Schück, F.: Zentralbl. f. Chir. **51**:1397, 1924.
20. Heidenhain, L., and Fried, C.: Klin. Wchnschr. **3**:1121, 1924.
21. Halberstaedter, L., and Simons, A.: Acta radiol. **5**:501, 1926.

tion caused delayed healing, though the ultimate scar tended to be smoother and more satisfactory from a cosmetic point of view. They noted also in one patient that after excision a malignant tumor recurred in the nonirradiated half of a wound but not in the irradiated half.

L. Freund [22] observed that when keloids, lupus vulgaris and similar lesions were removed surgically, treatment of the incision with unfiltered roentgen rays (dose about 6 to 7 Holzknecht units, or approximately 700 roentgens) assured a soft inconspicuous scar. His communication was brief, and no time intervals were mentioned. Bab [23] reported a similar experience.

Jüngling [24] reported observations concerning preoperative irradiation and postoperative radium treatment of carcinomas. After doses of from 720 to 900 roentgens, given in from four to five sittings, he noted a slight increase in the difficulty of operation in some cases on account of fibrosis, but no increase in many cases. Following radium implantation, immediately after operation, the only complications noted by him were small areas of necrosis in the wound and a slight serous discharge persisting over a moderate period. He stated that skin grafts took well in such cases. No histologic observations were reported.

Huwer,[25] in a short communication, recently discussed the giant cells found following irradiation of carcinoma of the uterine cervix. He stated that some of these are derived from connective tissue. It is evident, however, from his illustrations that he was dealing with foreign body giant cells, probably brought out by the presence of necrotic cancer tissue, and not with the fibroblastic giant cells under discussion here.

Dr. Bunting [26] has seen giant fibroblasts in x-ray burns submitted to him for histologic examination.

I noted fibroblastic giant cells in two cases coming to my attention. In the first patient, a woman treated with radium and high voltage roentgen therapy for carcinoma of the uterine cervix, an ulceration of the intestine occurred; in the granulation tissue of the ulcer malformed fibroblasts were present, resembling closely those seen in experimentally irradiated wounds.

The second case was that of a man with carcinoma of the bladder. Electric fulguration was performed, causing an intense inflammatory reaction, and radium emanation seeds were implanted. The patient died about a month later, and in the inflammatory tissue taken post mortem could be seen the same phenomenon as in the first case—fibroblastic giant cells.

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22. Freund, L.: Deutsche Ztschr. f. Chir. **222**:416, 1930.
23. Bab, M.: Deutsche med. Wchnschr. **57**:319, 1931.
24. Jüngling, O.: Strahlentherapie **44**:125, 1932.
25. Huwer, G.: Zentralbl. f. Gynäk. **54**:103, 1933.
26. Bunting, C. H.: Personal communication to the author.

The apparent contradictions in regard to the influence of roentgen irradiation on the healing of wounds arise, I believe, from two sources. First, the dose and method of application appear to be of great importance, the smaller doses having rather a stimulating effect, or at least causing no retardation, while a higher dosage comparable to that used in treating malignant tumors has a definite inhibitory influence on the repair process. Again the time interval is important, as discussed elsewhere.

Second, in investigations not including histologic examination a deceptive factor is introduced in the greater susceptibility of connective tissue as compared with that of epithelium. As previously mentioned, in our series of experimental wounds in the skin, several cases were noted in which the epithelium had entirely covered the wound, while the underlying connective tissue showed an almost entire lack of growth. Observed grossly, this would appear to be a perfectly healed wound, and might thus give rise to erroneous conclusions.

SUMMARY AND CONCLUSIONS

The results of an experimental investigation of the effect of roentgen rays on the healing of wounds are presented, with a brief review of the experimental and clinical literature on the subject.

The early histologic features found in such irradiated wound tissue are: (1) sluggishness of fibroblastic growth, (2) the presence of anomalous giant fibroblasts and (3) the persistence of a fibrin network for a varying period.

The first of these is considered to be most important from a practical point of view, and is most consistently seen when irradiation follows incision by approximately twenty-four hours. The second is the most constant characteristic, and since it has been noted also in human tissues subjected to roentgen and radium treatment, I think that its presence in inflammatory tissue is highly suggestive of a reaction to roentgen rays.

It is obviously improper to carry the results of animal experimental work bodily and in detail over into clinical practice; such an investigation can be seen in its true light only when thoroughly checked by clinical observation. Nevertheless, I think that enough evidence has accumulated to warrant the statement that roentgen irradiation in doses ordinarily used for the treatment of malignant tumors, administered within forty-eight hours after incision, may definitely retard healing but has no bad effect as far as ultimate results are concerned.

NOTE.—In the conversion of other units to roentgens, I have used the tables of T. C. Neeff (Strahlentherapie **33**:169, 1929).

CALCIFICATION OF THE SKIN IN DIABETES MELLITUS

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During the past few years abnormal calcification has attracted much attention among pathologists, clinicians and chemists. As far as we know, calcification never occurs in normal tissue, except in the formation of bone and in conditions spoken of as metastatic calcification. Any focus of dead or degenerated tissue that cannot be absorbed will probably become infiltrated with lime salts. Bearing these facts in mind, one is not surprised to find deposits of calcium in any organ of the body. Often the infiltrated tissue is dead, as in infarcts, caseous foci and inspissated collections of pus. Deposits of calcium may be found in inactive tissues, such as scar tissue, elastic tissue and ganglion cells of the brain which have become degenerated or necrotic. The scalp, muscle, myocardium, cardiac valves, arteries, veins, pleura, umbilicus, glands of internal secretion and prepuce have been found to be the site of deposits of calcium. Wiedman and Shaffer [1] reported a case in which calcium was distributed not only in the epidermis, but also widely throughout the corium, involving sweat glands and ducts, pacinian corpuscles and nerve trunks, as well as fibrous tissue of the corium.

Two forms of pathologic calcification are recognized. First, it occurs as a precipitation of calcium in secretions and excretions. This includes concretions in general, such as urinary and biliary calculi. Here we may explain the calcification by recognizable alterations in the composition of the secretion which leads to chemical precipitation. The second form is the type in which deposits of calcium salts are found in the tissues themselves, and is said by Bauer, Marble and Bennett [2] to be a rare condition affecting chiefly children. Langmead,[3] Versé,[4] Tisdall and Erb,[5] Morse [6] and Duret [7] reported cases occurring in children. Duret

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From the Laboratory of Pathology, New England Deaconess Hospital.

1. Wiedman, F. D., and Shaffer, L. W.: Arch. Dermat. & Syph. **14**:503, 1926.
2. Bauer, W.; Marble, A., and Bennett, G. A.: Am. J. M. Sc. **182**:237, 1931.
3. Langmead, F. S.: Arch. Pediat. **40**:112, 1923.
4. Versé, M.: Beitr. z. path. Anat. u. z. allg. Path. **53**:212, 1912.
5. Tisdall, F. F., and Erb, I. H.: Am. J. Dis. Child. **27**:28, 1924.
6. Morse, J. L.: Am. J. Dis. Child. **22**:412, 1921.
7. Duret, cited by Bauer and co-workers.[2]

noted occurrence of the condition in brother and sister. This type cannot be explained by a single factor or etiology. It is evident that several factors, both local and general, may be contributory to such conditions. Certain forms of tissue calcification are well recognized and are to be distinguished from the type which we are reporting.

Myositis ossificans or intramuscular and intermuscular formation of bone is probably the most common.[8] Under various pathologic conditions, bone is developed in the connective tissue in and between muscles. The formation of bone may begin in isolated muscles subjected to a single or repeated trauma or influenced by chronic inflammation in adjacent bones. As typical examples may be mentioned the formation of bone in the deltoid and pectoralis muscles, such as the so-called bayonettiers (bones from the impact of a gun), in the biceps of gymnasts and in the abductors of the upper thigh or of the vasti in horseback riders. Other forms of myositis ossificans, the etiology of which is obscure, are said to be more progressive and begin spontaneously, usually in early youth, first appearing in the muscles of the shoulder, the nape of the neck and the masseter muscles and then gradually spreading to the muscles of the back until all the muscles are involved. In some cases, malformations of the extremities, particularly microdactylia, have been observed. Probably the most widely accepted explanation is that there is a congenital, nonhereditary, reduced ability of differentiation of the connective tissue elements owing to a disturbance in the mesenchymal cells, and that as accompanying symptoms of the developmental inhibition there appear microdactylia and other malformations.

Metastatic calcification due to disease of the parathyroid glands is well known. Dawson and Struthers[9] reported a case of generalized osteitis fibrosa with tumor of the parathyroid gland (adenoma) and metastatic calcification. The calcification occurred in all organs and tissues of the body. Barr[10] stated that metastatic calcification has been observed several times in cases of hyperparathyroidism in which tumors of the parathyroid gland and osteitis fibrosa cystica have been associated. Collip, Clark and Scott[11] found that hypercalcemia may result from the administration of parathyroid hormone. Hubbard and Wentworth[12] observed metastatic calcification and hypercalcemia in a man with hyperplasia of the parathyroid gland. Hueper[13] found that dogs given injections of parathyroid hormone show deposits of calcium in the thyroid,

8. Kaufman, Edward: Pathology for Students and Practitioners, translated by S. P. Reimann, Philadelphia, P. Blakiston's Son & Co., 1929, vol. 3, p. 2051.
9. Dawson, J. W., and Struthers, J. W.: Edinburgh M. J. **30**:421, 1923.
10. Barr, D. P.: Physiol. Rev. **12**:593, 1932.
11. Collip, J. B.; Clark, E. P., and Scott, J. W.: J. Biol. Chem. **63**:439, 1925.
12. Hubbard and Wentworth: Proc. Soc. Exper. Med. **18**:307, 1921.
13. Hueper, Wilhelm: Arch. Path. **3**:14, 1927.

lungs, cardiac muscle, stomach—mostly in the fundus—duodenum and kidneys. Massive doses of viosterol have produced metastatic calcification.[14]

Rabl [15] suggested the theory that the metastatic calcification sometimes seen without lesions of the bone, as in the so-called calcium gout, may depend on renal lesions with decreased elimination of phosphoric acid. The retained phosphoric acid is buffered by calcium withdrawn from the bones, so that the blood contains an abnormally high content of calcium. Whenever the p_H of the blood is raised, as by the taking of food containing an abundance of bases, the excess calcium is deposited in the tissues. Wildbolz [16] Licharoff [17] and Lewandowsky [18] all agree that some forms of pathologic calcification are a disturbance of organic metabolism similar in character to gout, except that calcium salts are deposited instead of urates.

Durham [19] reported a case with extensive subcutaneous, periarticular and vascular calcification associated with chronic nephritis (small, granular kidney) in which the serum calcium was slightly below normal. The calcification here also involved veins, arteries, the mitral valve, the myocardium and ulcers of the leg.

Disorders of uric acid, fat or cholesterol metabolism may be closely related to some forms of abnormal calcification, but the relationship is not constant. The case of Bauer, Marble and Bennett [2] did not show an appreciable increase in uric acid, fatty acids or cholesterol.

Much attention has been given to the presence of iron in calcified tissues. Sprunt,[20] and later, Bennett [21] described cases of calcium and iron incrustation of the spleen. Both cases showed a predominance of iron and the presence of iron without calcium in some areas. Watts [22] demonstrated the association of these two substances in the choroid plexus and concluded that certain features suggested strongly that calcification follows thrombosis of the vascular supply to the plexus. Kockel [23] and Bittrolff [24] reported cases of calcium and iron incrustation of elastic

14. Hückel, R., and Wenzel, H.: Arch. Exper. Path. & Pharmacol. **141**:292, 1929. Smith, M. L., and Elvove, E.: Pub. Health Rep. **44**:1245, 1929. Shohl, A. T.; Goldblatt, H., and Brown, H. B.: J. Clin. Investigation **8**:505, 1930.

15. Rabl: Klin. Wchnschr. **2**:202, 1923; Virchows Arch. f. path. Anat. **245**: 542, 1923.

16. Wildbolz: Arch. f. Dermat. u. Syph. **70**:435, 1904.

17. Licharoff, cited by Pospelow.[30]

18. Lewandowsky: Virchows Arch. f. path. Anat. **181**:179, 1905.

19. Durham, R. H.: Ann. Clin. Med. **5**:679, 1926-1927.

20. Sprunt, T. P.: J. Exper. Med. **14**:59, 1911.

21. Bennett, G. A.: Arch. Path. **7**:71, 1929.

22. Watts, J.: Arch. Surg. **15**:89, 1927.

23. Kockel: Deutsches Arch. f. klin. Med. **64**:332, 1899.

24. Bittrolff: Beitr. z. path. Anat. u. z. allg. Path. **49**:213, 1910.

fibers in lungs which were the seat of chronic passive congestion. The lesions were in the walls of small blood vessels and in the elastic tissue of the alveolar walls. Ehrlich [25] noted several instances of simultaneous calcium and iron incrustation of elastic fibers in scars of splenic infarction, in intestinal polypi and in the alveolar walls of the lungs. He concluded that elastic fibers in the neighborhood of hemorrhage have a special tendency to absorb iron and that such fibers may secondarily become calcified. Rona [26] and Hektoen [27] mentioned the finding of calcium and iron containing elastic fibers in giant cells in various inflammatory processes. Gierke [28] called attention to the physiologic association of calcium and iron in the fetus, in which the entire skeleton as far as it has been calcified contains iron, with an excess in the parts of active ossification. There is a considerable amount of controversy as to whether the iron or the calcium is deposited first. Some investigators claim that iron is deposited first and acts as a mordant for the calcium.

The formation of calcium soap is an important step in the process of pathologic calcification, but it is not essential. Wells [29] found doubtful traces of calcium soap in calcifying matter and small amounts of other soaps of fatty acids. Calcium soap implanted in tissues does not become transformed into calcium phosphate and carbonate, but is chiefly absorbed and removed. Wells therefore feels that chemical precipitation in the tissues is not responsible for the calcification, but that the latter depends on a physicochemical factor and variation in the concentration of carbon dioxide.

Versé,[4] in referring to several cases of generalized calcium deposits, called attention to the early changes in the intercellular substance of connective tissue. Pospelow [30] mentioned the affinity between elastic fibers and calcium salts, and expressed the belief that the deposit can probably occur in normal elastic tissue. He considered that calcium may be deposited in abnormal locations, either because the blood is saturated with calcium or because the solubility of calcium in plasma is changed, even though the blood calcium is not above normal.

Bauer, Marble and Bennett [2] concluded that the basis of the disorder lies in an abnormality of calcium and phosphorus metabolism. An increased retention of calcium and phosphorus may be the result of a local cellular condition as yet undetermined. In their case the studies of calcium and phosphorus balance indicated a marked tendency to retain

25. Ehrlich, S.: Centralbl. f. allg. Path. u. path. Anat. **17**:177, 1906.
26. Rona: Beitr. z. path. Anat. u. z. allg. Path. **27**:349, 1900.
27. Hektoen: J. M. Research **7**:159, 1902.
28. Gierke: Virchows Arch. f. path. Anat. **167**:318, 1902.
29. Wells, H. G.: Chemical Pathology, ed. 5, Philadelphia, W. B. Saunders Company, 1925, p. 494.
30. Pospelow, W. A.: Arch. f. Dermat. u. Syph. **140**:75, 1922.

the absorbed calcium and phosphorus in spite of the normal blood calcium and phosphorus values. This was more marked for calcium than for phosphorus.

REPORT OF CASES

CASE 1.—An obese white woman, aged 66, was admitted to the New England Deaconess Hospital under the care of Dr. Elliott P. Joslin on May 15, 1932, with severe infection and gangrene of her left foot. She had had diabetes since 1918, and had received insulin therapy for the past three years. In August, 1929, she had a slight shock, involving the left arm and leg. This improved after ten days, but left some weakness which persisted. Three months before admission she noticed a festered area on the bottom of her foot. The condition improved with rest, but activity caused a discharge of a small quantity of pus. The infection

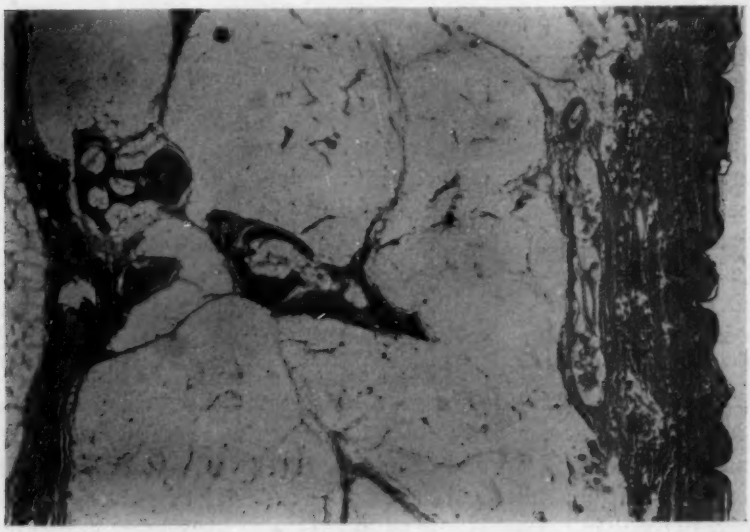

Fig. 1 (case 1).—Skin from the leg, showing deposits of calcium and the formation of bone in the subcutaneous tissue; decalcified; reduced from × 20.

was drained one week before admission by incisions on the plantar and dorsal aspects of the foot. There was a foul odor and a discharge of pus and gas through the plantar region. The circulation was fair except for the absence of pulsation in the dorsalis pedis.

On admission the temperature was 102 F.; the pulse rate, 110, and respiration, 23. On May 18, under spinal anesthesia, the left leg was amputated just above the knee. The postoperative course was good.

The urinary sugar was 0.2 per cent on admission. The amount of sugar gradually increased, until on the fifth day it was 4.4 per cent. The following five days the amount of sugar steadily decreased to 0 and remained so until the patient was discharged from the hospital. The Wassermann test was negative. The blood nonprotein nitrogen varied from 30 to 108 mg. per hundred cubic centimeters; the blood sugar, from 0.19 to 0.74. The carbon dioxide of the blood was 40 per

cent. Analysis of the blood on May 16, 1933 (one year later) showed: sugar, 0.24 per cent; calcium, 10 mg. per hundred cubic centimeters; phosphorus, 3.1 mg. and cholesterol, 291 mg.

The specimen consisted of a left leg amputated just above the knee. It weighed 5,800 Gm. There were two fairly recent surgical incisions, one 2 cm. long, located on the dorsum of the foot between the third and fourth metatarsals; the second, 6 cm. long, on the plantar surface in the center of the ball of the foot. From each could be expressed foul-smelling, grayish-yellow, moderately thick pus. The necrosis extended through the soft tissues and apparently involved the bones of the foot. The posterior tibial artery showed medial and intimal sclerosis with calcification. The anterior tibial artery was similar, except that the lumen was apparently occluded in its distal portion by atheromatous plaques. The nerves

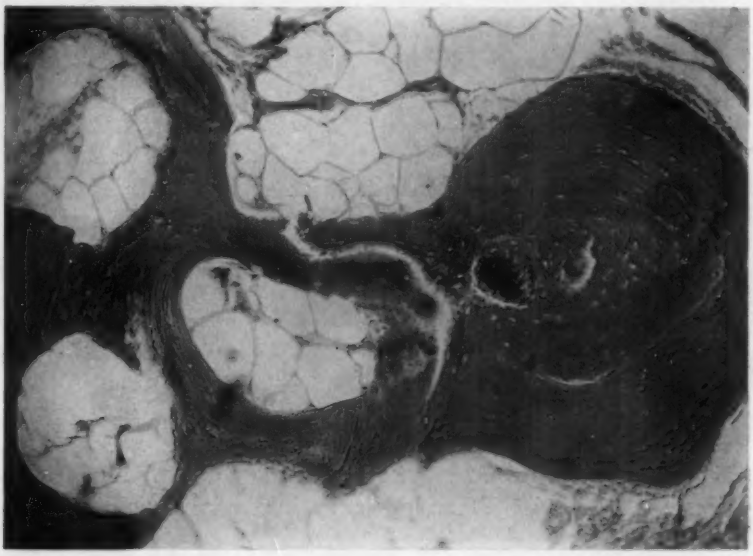

Fig. 2 (case 1).—Skin from the left leg showing bone with marrow spaces; decalcified; reduced from × 138.

and veins were not remarkable. In the subcutaneous tissue of the leg could be felt many small spicules of calcification. A section of skin and tissue from the foot showed an extensive infiltration of polymorphonuclear leukocytes with necrosis and gangrene. The lumens of the anterior and posterior tibial arteries were almost occluded by intimal plaques. There were some edema, a small amount of fat, calcium and cholesterol, and slight infiltration of the intima with lymphocytes and endothelial cells. The media was greatly thickened and contained a large amount of calcium and a few spicules of bone. There were also proliferation of connective tissue and profuse infiltration of lymphocytes and endothelial cells. The adventitia was not remarkable.

The epidermis of a section of skin from the leg was not remarkable. Deep in the corium and in the subcutaneous tissue could be seen spicules of bone with fatty marrow (figs. 1 and 2). There was apparently no inflammatory reaction

or degeneration of the tissues other than hyalinization and calcification of the elastic fibers. Some of the small veins showed hyalinization and calcification of the media (fig. 3).

The roentgen examination, by Dr. I. K. Bogan, showed numerous, irregularly linear, calcium shadows in the soft tissues anterior to the middle portion of the left tibia. Smaller rounded shadows were seen throughout the soft parts of the leg to within a distance of 2 inches (5 cm.) above the ankle joint. These had about the density of plaques seen in arteriosclerotic vessels, and lay in the subcutaneous tissues. The arteries of the leg showed calcification, 3+. There was calcinosis (fig. 4).

CASE 2.—A white woman, aged 66, was admitted for the first time to the New England Deaconess Hospital to the service of Dr. Elliott P. Joslin on July

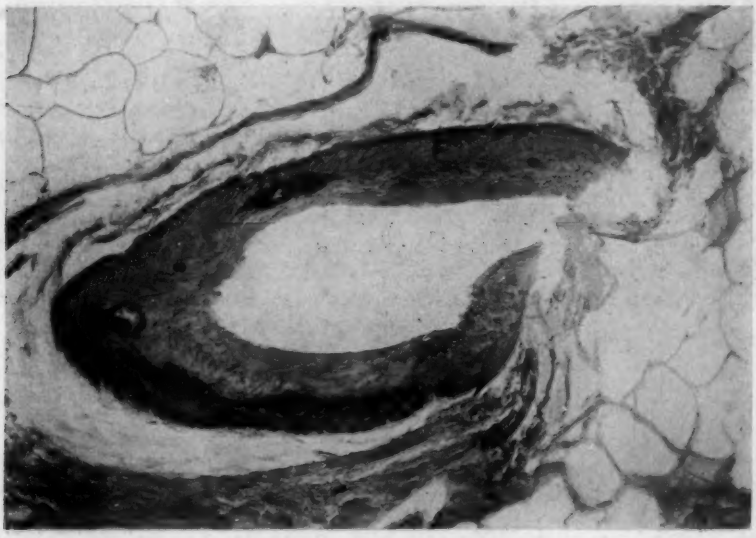

Fig. 3 (case 1).—Skin from the left leg. Vein showing calcification of the media; decalcified; reduced from × 150.

10, 1930, on account of diabetes mellitus and multiple and chronic infections of the right leg.

She had had diabetes since 1927. In February, 1930, she had an infection of the great toe of the right foot, and later an infection and a discharge from the fifth toe on the same foot; four weeks afterward severe pain developed in the calf of the right leg. About July 1, 1930, an ulcer developed on the calf of this leg.

On entrance, the right foot was edematous and red, and there was an ulcerated area about 4 cm. in diameter on the lateral aspect of the lower portion of the right leg. The blood pressure was 190 systolic and 100 diastolic. Culture from the ulcer showed Staphylococcus albus. The urinary sugar was 8 per cent on admission, but was reduced to 0 during the first five days; the blood sugar was 0.26 per cent on admission and 0.13 per cent when the patient was discharged.

Fig. 4 (case 1).—Roentgenogram of the left leg showing calcification of the skin. Reduced.

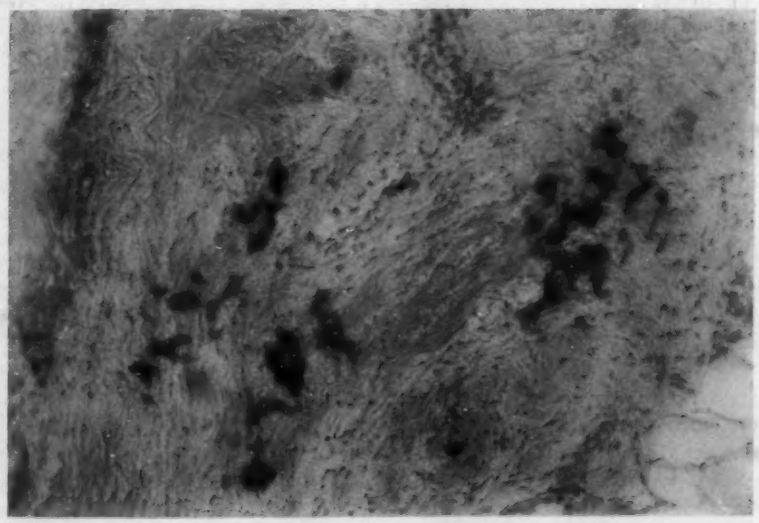

Fig. 5 (case 2).—Skin of the left leg, showing calcification; reduced from × 225.

The dosage of insulin varied from 5 to 15 units daily. The ulcer healed slowly. The fifth toe on the right foot was amputated on July 30. The patient was discharged on October 2, improved.

The specimen consisted of the fifth toe amputated at the level of the metatarsal phalangeal joint. The subcutaneous tissues were soft. The microscopic diagnosis was chronic osteomyelitis.

The patient was admitted the second time on May 11, 1931, on account of superficial ulceration of the left foot. Slight glycosuria was present on admission, but disappeared following the use of 5 units of insulin daily for a week; no further insulin was necessary. The ulcer healed slowly.

The patient was admitted the third time on Dec. 14, 1931, on account of an ulcer on the left foot and 4 per cent glycosuria. The glycosuria disappeared abruptly on the administration of 10 units of insulin. On December 23, the lower portion of the left leg was amputated. The patient was discharged improved.

The specimen consisted of the left leg amputated at about the midcalf. It weighed 1,270 Gm. The small toe was black and gangrenous on the superior and medial surfaces and the distal end. A section from the small toe was black. The posterior tibial artery was hard and contained a considerable amount of calcium. The lumen was occluded to a diameter of 1 mm. The anterior tibial artery was wirelike and contained a considerable amount of calcium. About 2 cm. below the point of amputation, the lumen was about 2 mm. in diameter. The microscopic diagnosis was: gangrene; arteriosclerosis, intimal and medial type; arterial thrombosis with organization and canalization, and slight chronic osteomyelitis.

The patient was admitted the fourth time on Aug. 10, 1932, with gangrene and infection of the right foot. The lower portion of the right leg was amputated on August 11. The patient made an uncomplicated recovery and was discharged improved.

The specimen consisted of the right leg which had been amputated at the midcalf. The weight was 1,190 Gm. The small toe had previously been removed and a well healed surgical scar remained. The skin of the adjacent toe was dry and wrinkled. The third toe was black and gangrenous. The second toe was similar to the fourth. The great toe had a gangrenous area at the tip, involving the nail-bed and measuring 2 cm. in diameter. On the anterior surface of the leg in the distal third was a hard, black, ulcerated area 1 cm. in diameter. The anterior tibial artery was hard and tortuous and showed extensive intimal thickening and calcification. The lumen was patent. The posterior tibial artery was similar except that the lumen appeared to be completely occluded. The microscopic diagnosis was: gangrene; arteriosclerosis, intimal and medial type, and acute secondary osteomyelitis.

The patient was admitted the fifth time on Feb. 6, 1933, on account of gangrene of the amputation stump of the lower portion of the left leg. Amputation was done at the midthigh on February 9. The urinary sugar on admission was 3 per cent and was soon reduced to 0. On February 16, the blood calcium was 10.1 mg. per hundred cubic centimeters; the cholesterol, 197 mg. The postoperative course was good. The patient was discharged on February 23, improved.

The specimen consisted of a portion of the left leg. The secondary amputation was made from the midcalf to the midthigh. The distal end contained a hard, black, gangrenous area about 9 cm. in diameter, partially covered with a brown crust. At the distal end of the posterior tibial nerve was a small tumor mass 0.5 cm. in diameter, firm and white. The arteries were markedly sclerosed and calcified. On section of the knee joint, the articular cartilages showed erosions, marked overgrowth and calcification along the edges. One of the sections showed

extensive necrosis and gangrene with the deposition of small and large foci of calcification. In some of the sections deposits of calcium were found in areas in which there was no evidence of inflammation or degeneration other than hyalinization and calcification of the connective tissue. Some of the calcium appeared as small, basic-staining granules (about 1 micron in diameter) scattered rather diffusely throughout the corium and subcutaneous tissues. Other deposits were much larger and apparently represented a conglomeration of the small granules. The femoral and posterior tibial arteries contained large intimal plaques with an infiltration of endothelial cells and accumulation of some fat, cholesterol and calcium. The media was thickened and contained a considerable amount of calcium. The adventitia and veins were not remarkable. A diagnosis of gangrene, arteriosclerosis (chiefly medial) and slight calcification of the corium was made.

The roentgen report, by Dr. I. K. Bogan, on February 16, showed that the vessels of the left leg and of the thigh and upper portion of the right leg showed extensive calcification. A linear area of density was seen internally, opposite the right knee joint, which was compatible with the presence of calcium in the skin.

COMMENT

In the two cases presented the patients were women, each 66 years of age with a history of diabetes for fourteen and six years, respectively. The clinical course of each did not differ from that of diabetic patients who do not show deposits of calcium in the tissues. In both cases the blood chemistry was not remarkable for diabetic patients, and the calcium was within normal limits, as was the cholesterol in case 1. It was not possible to make additional studies.

There was no evidence of any abnormality of the parathyroid glands. The patients did not receive viosterol. If impaired circulation was a factor, it is surprising that this lesion has not been found in others of the many gangrenous legs examined in this laboratory. Evidence of significant renal lesions was lacking. It is possible, though unlikely, that the inflammatory process in the gangrenous foci may have influenced the deposition of calcium in case 2, yet, according to the roentgen report, there were deposits of calcium in the corium at least 15 cm. from the zone of inflammation. In case 1 the calcification was even farther from the focus of inflammation.

SUMMARY

Unexplained calcification of the subcutaneous tissues and corium was found in two elderly diabetic patients. The usual causes for metastatic calcification have been ruled out.

AN ANATOMIC MECHANISM IN THE PRODUCTION OF THE FLINT MURMUR

MAURICE ROSENTHAL, M.D.
BROOKLYN

In 1862, Flint [1] reported two cases of aortic insufficiency in which a presystolic blubbering murmur occurred in the mitral area. At autopsy an insufficiency of the aortic valves was established, but no lesions of the mitral valves were found to account for the well marked mitral presystolic murmur. In explanation, Flint suggested a floating up of the mitral leaflets with the filling of the left ventricle, and since in cases of considerable aortic insufficiency, the left ventricle is rapidly filled with regurgitant blood from the aorta as well as from the auricle, the distention of the ventricle might be such that the mitral curtains are brought into coaptation. When auricular contraction then takes place, the mitral direct current passing between these curtains throws them into vibration and gives rise to the characteristic blubbering murmur. Flint considered the physical condition in effect analogous to a contraction of the mitral orifice from an adhesion or an approximation and fixation of the curtains at their sides, such as in organic mitral stenosis gives rise to the mitral direct murmur of similar character.

Herrmann,[2] in reviewing the significant historical facts concerning the discovery and explanations of the Flint phenomenon, mentioned the original and various modified explanations of the mechanism as offered by Sansom,[3] Phear,[4] Gibson,[5] Broadbent,[6] Guiteras,[7] Da Costa,[8] Futcher [9] and Huffman.[10] Herrmann pointed out that in experimental animals

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1. Flint, Austin: Am. J. M. Sc. **49**:29, 1862; **91**:35, 1886.
2. Herrmann, George R.: Am. Heart J. **1**:671, 1926.
3. Sansom, A. E.: The Diagnosis of Disease of the Heart and Thoracic Aorta, London, C. Griffin & Co., 1892, p. 385.
4. Phear, A. G.: Lancet **2**:716, 1895.
5. Gibson, G. A.: Diseases of the Heart and Aorta, Edinburgh, Y. J. Pentland, 1898, p. 497.
6. Broadbent, W. H.: Heart Disease, New York, William Wood & Company, 1900, p. 150.
7. Guiteras, J.: M. News **47**:533, 1885; Tr. A. Am. Physicians **11**:37, 1887.
8. Da Costa, J. C.: Physical Diagnosis, Philadelphia, W. B. Saunders Company, 1913, p. 310.
9. Futcher, T. B.: Outlines of Physical Diagnosis, Baltimore, Students' Book Store, 1920, p. 63.
10. Huffman, O. V.: M. Rec. **93**:681, 1918.

lesions of the posterior cusps, especially extensive puncture wounds near the basal attachments, are most likely to produce the phenomenon. He also described the cases of two persons who presented the Flint phenomenon during life and who showed incompetency of the posterior aortic cusps at autopsy.

A review of the literature on the subject leaves the impression that knowledge of the mechanism still remains unsatisfactory and vague. The following two cases are presented, since in them a definite organic lesion, not involving primarily the mitral valve, seems to offer a definite and concrete explanation for the Flint murmur that was observed during the life of these two persons.

REPORT OF CASES

CASE 1.—A white man, aged 25, entered the Long Island College Hospital complaining of chills and fever and of pains in the legs. His past history for the most part was irrelevant. He had scarlet fever at the age of 4 years, and had never had rheumatic fever, tonsillitis, diphtheria, typhoid fever or pneumonia. He said that he had never had syphilis or gonorrhea. The present illness dated back about a month before admission, when he experienced sharp pains in his arms and legs. He continued to work until two weeks before admission, when he had a severe chill and fever. Several days before admission he became drowsy and nauseated. On admission he complained of headache, dizziness and pains in the extremities.

Examination showed a fairly well developed and nourished young man, apparently 25 years of age, lying in bed and in no respiratory distress. The lips and nails were cyanotic. Numerous petechiae were scattered over the neck, face and thorax. The apical impulse of the heart was seen and felt in the fifth interspace. The sounds were of good quality. Examination of the heart revealed only a presystolic blubbering murmur in the mitral area. No signs of aortic regurgitation were present on admission. The blood pressure was 110 systolic and 70 diastolic. Examination of the lungs revealed nothing of significance. The abdomen was soft and very full and had many petechial spots. The splenic and hepatic edges were not palpated. The Wassermann reaction was negative. A culture of the blood revealed 136 colonies of Streptococcus viridans per cubic centimeter. The urine showed a large quantity of albumin, numerous white blood cells and red blood cells and coarse granular casts. Two days after admission signs of aortic regurgitation suddenly developed, and the late diastolic murmur at the mitral areas was still present. The blood pressure was 120 systolic and 40 diastolic. The patient's condition gradually became worse, and he died nine days after admission.

Autopsy showed the following: The lungs were moderately congested. The liver was normal in size, weighing 1,650 Gm., and the lower edge was slightly rounded. On section, a moderate degree of passive congestion was noted. Examination of the gastro-intestinal tract revealed nothing of pathologic significance. The spleen was enlarged, weighing 500 Gm., and scattered over its surface several yellow infarcted areas were found. The kidneys were normal in size and shape and quite firm in consistency. Their capsules stripped with ease. Several small infarcted areas from 1 to 2 cm. in size were found in both kidneys. The pericardial sac contained 30 cc. of clear yellow fluid. There was no exudate on the epicardial or pericardial surfaces. The heart was normal in size and shape, weighing 300 Gm. The muscle of the left ventricle was firm in consistency. When this

chamber was opened the mitral leaflets were normal. They were not thickened, shortened or grown together. The chordae tendineae were not thickened or shortened. There was no stenosis of the ostium or insufficiency of the valve. On examination of the aortic valve a large vegetation 2 cm. in diameter was found suspended from the base of the posterior cusp, and a large perforated window of the cusp was also noted. A vegetation 1 cm. in diameter was also found on the right anterior cusp. The cusps were not thickened, grown together or retracted; that is, no evidence of a previous endocarditis was found. The remaining cardiac valves were normal (fig. 1).

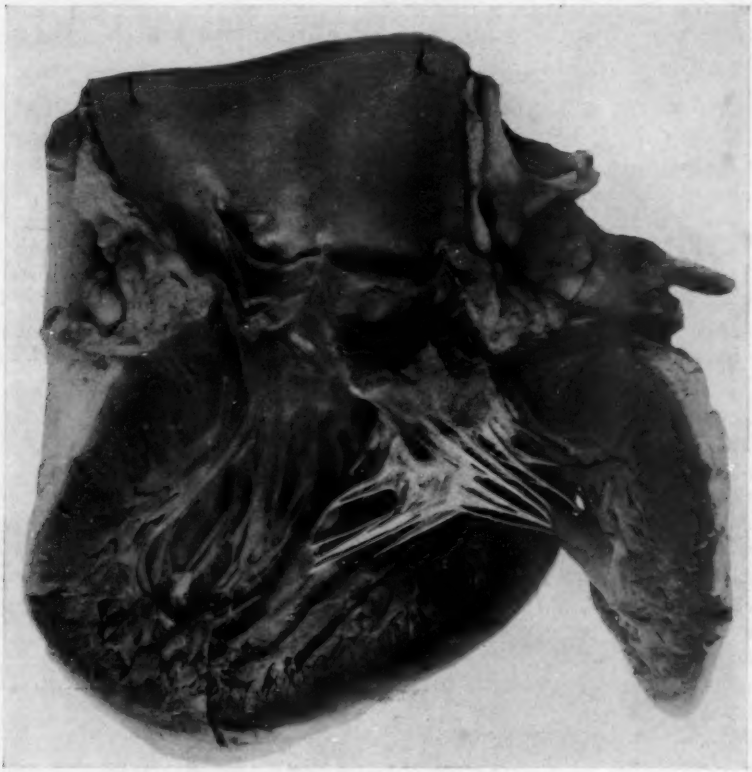

Fig. 1 (case 1).—The normal mitral leaflet is seen, and near its attachment the vegetations on the aortic valves are visible. The interference produced by these vegetations in the function of the anterior leaflet of the mitral valve is shown in figure 2.

Case 2.—A white woman, aged 44, was admitted to the Long Island College Hospital complaining of swelling of the ankles, dyspnea, precordial pain and vomiting. The family history was irrelevant. She had rheumatism at 11 years of age and was sick for three months, recovering without complications so far as she knew. She had malaria at 16 years of age, whooping cough at 21 years, and pneumonia three times between the ages of 27 and 30 years, recovering from all without complications. She said that neither she nor any one of her several

husbands had ever had a venereal infection. The present illness began six months before admission; following a severe cold, she collapsed on the street complaining of severe dyspnea, palpitation and dizziness. After two months' rest in bed she recovered sufficiently to be able to swim and dance and felt entirely well. Two months later she experienced a similar attack and was admitted to a hospital where she remained for six weeks. During her hospitalization a roentgenogram was taken, and she was told that she had a pericardial effusion. A few days after discharge from the hospital a peritonsillar abscess developed which ruptured spontaneously. She then suffered a return of her previous symptoms and was admitted to the Long Island College Hospital with the complaints noted.

Examination showed a well developed and nourished woman. There was moderate cyanosis of the lips and nail-beds. The patient was orthopneic. Her pupils were slightly unequal but regular and reacted to light. The throat was moderately injected, and the tonsils were small and ragged and appeared infected. The veins of the neck were full when the patient was erect in bed. The apical impulse was localized in the sixth interspace in the anterior axillary line. The cardiac rhythm was completely irregular. A thrill was felt over the apex, apparently presystolic, although the time was uncertain. Systolic and diastolic murmurs were heard at the base. After a short course of quinidine therapy, the cardiac rate became regular, and at this time a late rumbling diastolic murmur was heard at the mitral area in addition to the to and fro murmurs at the base. The family physician also had reported hearing a presystolic murmur in the mitral area on certain occasions. The pulse was of the Corrigan type. The blood pressure was 140 systolic and 35 diastolic; the temperature 100 F.; the pulse rate, 90, and respiration, 23. The abdomen showed tenderness in the right upper quadrant. Breath sounds were vesicular throughout both lungs, except at the right base where many subcrepitant râles were heard. The blood count showed: red blood cells, 3,800,000; hemoglobin, 75 per cent; white cells, 10,500, and polymorphonuclears, 71 per cent. Urinalysis showed a specific gravity of 1.028 and a faint trace of albumin. There were no acid bodies or reducing substances, and the sediment did not contain formed elements. The Wassermann and Kahn reactions of the blood were 4 plus. In the electrocardiograph, the Q R S groups were slurred in all leads; the T waves were inverted in lead I, indicating ventricular myocardial disease. The blood culture was negative. Several days later the patient died of cardiac failure.

Autopsy disclosed the following: There were hemorrhagic infarcts in the lower lobes of both lungs. Emboli were present in the branches of both right and left pulmonary arteries. The liver showed fatty degeneration and moderate passive congestion. The kidneys showed cloudy swelling and fatty degeneration. The peritoneal surface was covered by a scanty amount of fresh fibrinous exudate. Infarction of the transverse and descending colon and thrombosis of the superior mesenteric vein were found. The heart was enormously enlarged, weighing 600 Gm., as the result of marked hypertrophy and dilatation of the left ventricle and hypertrophy and moderate dilatation of the right ventricle. The epicardial surfaces were smooth and glistening. The mitral valve was normal. There was no stenosis of the ostium or insufficiency of its leaflets. The aorta and the aortic valves were the seat of a syphilitic aortitis and sclerosis. The syphilitic process in the aorta involved the entire arch but was most marked in the ascending portion and sinuses of Valsalva. A great deal of sclerosis and calcification were also found in this area. The aortic valve cusps were markedly thickened, shortened and retracted. Their edges were rounded, and there was a slight separation of two of the commissures. The posterior cusp was unusually rigid and calcified in the diastolic phase, thus projecting into the aortic lumen. Both of the coronary

orifices were patent. At the level of the aortic ring the vessel measured 9.5 cm. in circumference. The valve was both relatively and absolutely insufficient. The tricuspid and pulmonary valves were grossly normal. The coronary arteries were moderately sclerotic, but there was no evidence of coronary occlusion.

COMMENT

My attention was first drawn to the possibility that an organic lesion might be the mechanism for the production of a Flint murmur while I was working in Vienna under Prof. J. Erdheim. There I had the opportunity to study at autopsy several cases in which the Flint murmur had been heard, and I was impressed by the fact that in these cases, associated with the aortic insufficiency, there occurred as a part of the aortic involvement vegetations of large size on the posterior aortic cusp. The first case described in this report is of such a nature, while in the second the same mechanical effects were produced by another sort of aortic lesion. The common factor and the method by which it produced the Flint murmur would seem to be as follows:

During the systolic contraction of the left ventricle, the aortic cusps with any vegetation that may be superimposed on them are forced up into the aorta. During diastole the valves recede, projecting outward and downward, and attempt to approximate along their ventricular surfaces. Under these conditions a vegetation suspended from the ventricular surface of the posterior aortic cusp will rest on or near the endocardial surface of the ventricle. This vegetation is now occupying the normal diastolic mural position of the anterior leaflet of the mitral valve. Therefore, the vegetation does not permit the anterior mitral leaflet to rest on or near the ventricular wall, but instead holds it up and at the same time produces a bulge with the formation of a culdesac on the auricular surface of the anterior flap of the mitral valve. It is this deformity of an otherwise intact mitral leaflet that produces the eddies and currents which give rise to a Flint murmur (fig. 2).

In case 1 such a mechanism occurred, and it is to be noted that the presystolic murmur was present before signs of aortic regurgitation occurred. This fact strongly suggests that it was the vegetation on the posterior aortic cusp that played the important rôle in the mechanism of the Flint murmur and not the regurgitation which later occurred with the progress of the destructive lesion. The latter is the mechanism suggested by Herrmann,[2] although he mentioned that bulging of the posterior segment may in some instances encroach on the mitral orifice and at least at times contribute some to the obstruction of the orifice.[11]

11. In reviewing one of Herrmann's earlier contributions (Am. Heart J. **1**:485, 1926), one is impressed with the fact that the Flint phenomenon occurred in 20 per cent of the dogs with experimental aortic insufficiency and that spontaneous endocarditis also appeared in 20 per cent of the experiments.

In cases of healed endocarditis or arteriosclerosis of the aortic cusps and occasionally in syphilis of the aorta in which the aortic cusps are secondarily involved as a result of the syphilitic valvulitis, the secondary changes of sclerosis and calcification that have taken place in the valve cusps cause them to project into the lumen of the aorta, since they are calcified in a permanent diastolic phase. The same sort of deformity of an intact mitral leaflet as that described in the first case may therefore be produced, as was observed in the case of the vegetative lesion. Thus in case 2 it was demonstrated at necropsy that when the anterior mitral leaflet was in its diastolic position a bulge and a culdesac were produced on the auricular surface of the anterior mitral leaflet by the calcified projecting posterior aortic cusp.

In considering the description of the Flint murmur as it is given in textbooks and in published reports, one is impressed with the fact

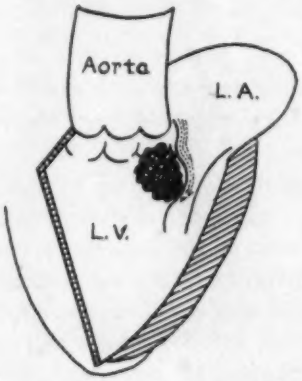

Fig. 2.—Diagrammatic representation of the relation of the vegetative mass on the aortic valves to the intact anterior leaflet of the mitral valve. The culdesac and eddies produced by it account for the Flint murmur.

that the term "blubbering presystolic murmur" has been much overused if not abused and has come to be a rubber-stamp expression that is commonly applied to a large and poorly defined group of audible phenomona. Phear,[4] who studied many cases both clinically and pathologically, mentioned that the murmur may occupy the beginning, middle or end of the diastolic period. Osler [12] spoke of it as extremely variable in intensity, disappearing and reappearing without apparent cause. In this regard it is apparent that by my interpretation of the mechanism of its production differences in the size and position of the vegetation on the aortic valve in its relation to the anterior mitral leaflet would necessarily cause a variation in the size and position of the culdesac on

12. Osler, W.: Principles and Practice of Medicine, ed. 3, New York, D. Appleton and Company, 1898, p. 714.

the auricular surface of the mitral leaflet. This variation in size of the vegetation, due to rapid growth in some cases and partial or total loss from embolization or rupture of aortic cusps in others, would explain the extreme variability of the murmur and particularly its disappearance and reappearance.

Although the original and the previously given modified explanations of the mechanism of the Flint phenomenon are possible, they are not based on demonstrable pathologic and anatomic changes, and this fact, associated with the vagueness of the clinical definition of the murmur, greatly weakens the value of this phenomenon for the clinician. If only one type of this murmur, therefore, can be established as caused by variation in anatomic structure, such as is described in my two cases, it would seem that it can be definitely removed from the group of poorly understood functional murmurs and included in that of the important organic murmurs of morphologic significance.

CONCLUSIONS

One cause of the Flint murmur is a mechanical deformity or distortion of an otherwise essentially normal anterior flap of the mitral valve.

The deformity consists of a bulging of the anterior mitral leaflet with the formation of a culdesac on the auricular surface. This may be produced by a vegetation on the posterior aortic cusp or by a calcified posterior cusp stiffened and fixed in its diastolic phase.

Various aortic diseases may produce this deformity, such as bacterial infection, active or healed, arteriosclerosis and occasionally syphilis of the aorta, if it is complicated by secondary involvement and sclerosis of the aortic cusps.

Laboratory Methods and Technical Notes

A NEW NEGATIVE MASS FOR MAKING ACCURATE PLASTIC REPRODUCTIONS

PAUL GROSS, M.D., CLEVELAND

The method of Poller[1] enables an amateur with only a moderate amount of skill to make presentable plastic reproductions of any part of the body and of inanimate objects with a surprising degree of accuracy and minuteness of detail. The method has the following advantages over other methods: It is simple and easy to execute. Irregularities and undercutting in the contours of the object to be reproduced, even though of high degree, do not hamper the worker. Indeed, often it is possible to make a one-piece mold. It does not require any preparation of the skin and will not tear out hair. It is possible to reproduce the face of a living person with the eyes open. The preparation is sterile and is applied at body temperature. The method can therefore be used to reproduce open lesions. It has, however, been commercialized; the formulas have been kept secret and the materials made expensive.

It is the purpose of this paper to present a different and new negative mass which is cheap and easily prepared and which yields satisfactory results.

PREPARATION OF THE NEGATIVE MASS

The negative mass consists of agar, magnesium soaps, absorbent cellulose wadding and water in the following proportions:

Material	Parts by Weight
Agar	100
Oil soap	100
Magnesium sulphate	40
Absorbent cellulose wadding*	12
Water	700-800
	(this is variable; see text)

* The cellulose wadding from the so-called sanitary napkins or pads was used.

The agar is heated in about 2,000 cc. of water until it is completely dissolved. The cellulose wadding is macerated in hot water until the fibers have separated. It is then thoroughly stirred into the hot agar. The oil soap is next added, and when it is completely dissolved and incorporated into the agar mass, a concentrated solution of the magnesium sulphate is slowly poured into it. At the same time, the mass is vigorously stirred. This precipitates the insoluble magnesium soaps. The

From the Laboratory of Charity Hospital and the Institute of Pathology, Western Reserve University.

1. Poller, A.: Das Pollersche Verfahren zum Abformen, Berlin, Urban & Schwarzenberg, 1931; Deutsche Ztschr. f. d. ges. gerichtl. Med. **13**:391, 1929. Iglauer, S.: Laryngoscope **42**:774, 1932. Kaempfer, L. J.: Hygeia **10**:636, 1932.

mass solidifies at about body temperature. The solid material is chopped fine or, preferably, ground in a food grinder. Since this mass contains from two and one-half to three times too much water, it is spread out thinly on paper and allowed to dry at room temperature to a state in which the crumbs are distinctly moist but no water can be expressed. The material is then ready for use.

Fig. 1.—Death mask cast in plaster of paris out of a one-piece mold. This illustrates the minuteness of detail obtainable.

Fig. 2.—Skull of an anencephalic fetus cast in plaster of paris out of a three-piece mold. The skull to the left is the original. The plaster of paris copy is to the right. This illustrates the use of a relatively simple mold to reproduce a very complicated rigid structure.

PREPARATION OF THE MOLD OR NEGATIVE

The ground material is heated in an enameled pan or dish under constant stirring to avoid burning. The consistence is adjusted by adding water or by evapora-

tion to that of a moderately thin paste which will allow itself to be applied with a brush without lumpiness and yet be viscous enough not to flow off dependent surfaces. The first layer of the material is applied thinly with a heat-resistant brush [2] at a temperature which produces no discomfort when applied to the cheek. Weak, fragile surfaces such as the hairy scalp are best first brushed delicately with a thinner, more fluid mass to stiffen the surface which will support the subsequent thicker negative mass. After the surface has been well covered with the agar mass by means of the brush, the proper thickness of the mold (from 2 to 4 cm.) is obtained more expeditiously by applying the material with a spatula. Depending on the size of the mold and the thickness of its wall, it may be necessary to reenforce it in order to avoid distortion. A sufficiently thick coat (from 5 to 10 mm.) of plaster of paris has been found satisfactory. No attempt should be made to remove the mold until the agar mass has completely hardened. The removal should be done with care and the vacuum broken gradually. Since the agar mass tends to lose water to the air, distortion is likely to result unless the positive is made within a reasonable time or unless the mold is kept properly moist.

Absorbent surfaces must be made nonabsorbent by painting with paraffin-benzene solution or other means to prevent the negative material from adhering. Similarly, if formaldehydized material is to be modeled, the specimens must first be washed free from formaldehyde. Then the surface is coated with glycerin or linseed oil in order to facilitate separation of the mold from the specimen. When a complete hand is to be modeled, the mold can be slipped off like a glove, since the agar mass is resilent. It is advisable to make cuts into the medial and lateral borders of the mold at the wrist previous to an attempt to remove the mold from the hand. Adult feet, entire heads, arthritic hands and other complicated structures are best made by splitting the mold into component parts, removing these components separately and reassembling them. The manner of splitting a mold must be left to the discretion of the worker. It is suggested that this be done by placing strong threads in appropriate positions before the agar mass is applied, and cutting the solidified agar mass by means of these. It occasionally occurs that in removing the mold from the original, pieces of the mold crack off. These pieces are replaced and fastened by means of long, slender pins, such as those used for mounting insects.

PREPARATION OF THE POSITIVE OR CAST

Plaster of paris has been used more than any other material for the positive, largely because of its cheapness. It has its disadvantages, but on the whole this material has proved satisfactory. When working with plaster of paris, it is necessary to adjust the fluidity so that it can be poured into and out of the mold several times and yet is not so thin as to entrap tiny air bubbles in doing so. Enough time must be given for the plaster to set, since the plaster in contact with the agar mass sets slowly, and premature removal of the mold may destroy the finer details. Red sealing wax has also been used successfully. It is rendered more fluid by the addition of a small amount of turpentine, which also lowers the melting point of the substance. The addition of an excessive amount of solvent renders the sealing wax soft and sticky. It seems likely that white sealing wax, though more expensive, would be more satisfactory, since it can be tinted by the addition of pigments and is more easily painted. The sealing wax is painted on the impression surface with a heat-resistant brush at a temperature which is no higher than is necessary to

2. A brush the bristles of which will not fall out and will remain moderately stiff in hot water.

keep the sealing wax at the proper fluidity. Paraffin has also been used. The agar mass separates easily from the positive. If the cast possesses markedly undercut surfaces, the mold is usually broken in removing the cast, and it becomes difficult to make a second cast from the same mold.

After use, the agar mass is ground up and stored in moisture-retaining containers until it is to be used again. The limit to the number of times that the agar mass can be reused has not been found.

COMMENT

The salient features of the method lie in the resiliency and other properties of the agar negative mass. Agar alone is too fluid to remain on dependent surfaces and tends to fracture too easily. To remedy the tendency to fracture, the absorbent cellulose wadding is introduced. Examination of a fractured surface of the negative mass discloses innumerable fine fibers of cellulose protruding, which act as a binding agent. This material also diminishes the tendency of the agar to flow. In preliminary experiments, a coarse material, such as chalk, was used to give the mass more body. However, chalk impaired the resiliency of the mass and made it more friable. Magnesium soaps were found satisfactory. At room temperature, the magnesium soaps are sticky solids which, when precipitated about cellulose fibers, will closely bind these together. At high temperatures, the soaps become fluid. It appears that the magnesium soaps not only give body to the mass, but also add to its strength.

SUMMARY

A method for making accurate plastic reproductions is described in which the negative material is cheap and easily prepared. The negative material consists of an agar-gel-soap-cellulose wadding mixture. The advantages of this method are enumerated. The positive can be cast in plaster of paris or paraffin, or made of resinous compounds such as sealing wax. The negative material can be used repeatedly.

Notes and News

University News, Promotions, Resignations, Appointments, Deaths, etc.—J. P. Simonds, professor of pathology in Northwestern University, has accepted the appointment as state chairman for Illinois of the American Society for the Control of Cancer.

Robert Rössle, professor of pathology in the University of Berlin, is now the editor of *Virchows Archiv für pathologische Anatomie und Physiologie und für klinische Medizin.*

Lee Foshay has been made associate professor of research bacteriology in the college of medicine of the University of Cincinnati.

Nathan Chandler Foote, formerly professor of pathology in the University of Cincinnati, is now professor of surgical pathology in Cornell University Medical College, New York, and surgical pathologist to the New York Hospital.

Amos C. Michael has been appointed instructor in pathology in the medical school of the University of Indiana at Indianapolis.

Louis H. Braafladt, formerly professor of pathology in Shantung Christian University, Tsinanfu, China, and recently hospital pathologist in Minot, N. D., died in North Sacramento, Calif., on Nov. 10, 1933, of staphylococcic septicemia, at the age of 48.

Emile Roux, the last to survive of Pasteur's collaborators, and the most intimate, died on Nov. 3, 1933, at 80 years of age. He was Pasteur's preparator from 1878 to 1883. In 1904 he followed Duclaux as director of the Pasteur Institute in Paris. With Yersin he discovered diphtheria toxin in 1888 and thus made possible the discovery of diphtheria antitoxin by Behring. Of extreme simplicity, he devoted himself unreservedly to carrying forward microbiologic investigation in Pasteur's spirit.

Pathologic Institutes Opened.—The Mallory Institute of Pathology of the Boston City Hospital was opened formally on Dec. 13, 1933. In the evening a dinner took place in honor of Frank B. Mallory.

The Algernon Firth Pathological Institute of the University of Leeds has been opened. The institute includes departments of pathology, bacteriology and cancer research. It is hoped that a pathologic museum may be added later.

Award for Essay on Goiter.—The American Association for the Study of Goiter offers $300 for the best essay based on original research on any phase of goiter, presented at the annual meeting in Cleveland, June 7, 8 and 9, 1934. Manuscripts, in English, must be submitted to the corresponding secretary, J. R. Young, M.D., 670 Cherry Street, Terre Haute, Ind., not later than April 1, 1934.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

THE THYROID GLAND OF THE WHITE RAT EXPOSED TO COLD. A. T. KENYON, Am. J. Path. **9**:347, 1933.

Exclusion of light for periods of from ten to twenty-five days did not produce striking changes in the thyroid gland of the rat. In confirmation of the work of Cramer, Ludford and Mills, exposure of rats to cold for from ten to twenty-five days produced hypertrophy, hyperplasia, loss of colloid and increased vascularity in the thyroid gland. Iodine in doses of 10 y (gamma 0.001 mg.) daily diminished or prevented the change. Hypertrophy and loss of colloid in general mean preponderant excretion of the hormone from the thyroid gland, arising either from impaired formation or from excessive excretion of the hormone. The actual amount excreted must be determined on physiologic grounds. There are no good reasons for supposing that impaired formation of the hormone occurred in these experiments. It is likely that the hypertrophy and loss of colloid herein described signify that the thyroid gland was excreting more of its hormone, but the essential demonstration by the tissues of increased need for thyroxine is as yet lacking.

AUTHOR'S SUMMARY.

INFLUENCE OF VARIATIONS IN FLUID INTAKE ON INTRACRANIAL PRESSURE IN "EPILEPTICS." FRANK FREMONT-SMITH and H. HOUSTON MERRITT, Arch. Neurol. & Psychiat. **29**:454, 1933.

Fremont-Smith and Merritt studied the effect of rapid drinking of large quantities of water on the intracranial pressure when diuresis is normal or inhibited. They also studied the effect of excessive and limited amounts of drinking fluids on the intracranial pressure in patients suffering from repeated generalized convulsions. They concluded that the cerebrospinal fluid pressure was not appreciably influenced by rapid drinking of large amounts of water when diuresis was normal, but when the excretion of urine was prevented by pitressin, a definite rise in the intracranial pressure was obtained. In prolonged periods of liquid intake, no rise of spinal fluid pressure was obtained from ingestion of large quantities of water, for the kidneys regulate the large or small intakes. No decrease in pressure was caused by restriction of fluid intake. Restriction of fluids may cause diminution of the number of epileptic attacks, though the authors believe that this diminution is brought on by the variations in the cerebrospinal fluid pressure.

G. B. HASSIN.

DEVELOPMENT OF THE MENINGES. SAMUEL C. HARVEY, HAROLD S. BURR and ERNEST VAN CAMPENHOUT, Arch. Neurol. & Psychiat. **29**:683, 1933.

By implantation of the prosencephalons of chicks on the allantois of a one hundred and ninety-two hour host without and with neural crest cells, selective staining of the neural crest with Nile blue sulphate and heteroplastic transplantations of the neural crest of the frog, the authors tried to add new proofs that the pia is an ectodermal structure derived from the neural crest, and that the pachymeninx is a mesodermal formation derived from the mesenchyme.

G. B. HASSIN.

THE SUBDURAL SPACE AND ITS LININGS. TIMOTHY LEARY and EDWARD A. EDWARDS, Arch. Neurol. & Psychiat. **29**:691, 1933.

Comparative studies of the scraped linings of the pericardium, pleura and subdural cavity convinced Leary and Edwards that the structures of the fore-

going cavities are not alike, that the dura is lined by fibroblasts and not mesothelial cells and that the arachnoid portion of the subdural space is covered by ectodermal cells.

G. B. HASSIN.

RECOVERY OF SENSATION IN DENERVATED PEDICLE AND FREE SKIN GRAFTS. F. E. KREDEL and J. P. EVANS, Arch. Neurol. & Psychiat. **29**:1203, 1933.

Kredel and Evans utilized skin grafts in their transplantations for the study of regeneration of nerves. The question as to whether a divided nerve regenerates from the central or peripheral stump has been extensively studied histologically, mainly in animals. The studies of Kredel and Evans are practically the only careful observations along these lines in human beings, and they furnish an indirect proof of the correctness of the central theory of regeneration of nerves. The free as well as the pedicle skin grafts (on the lips and the extremities) showed in seventeen of eighteen cases studied a return of the various sensations—pain, temperature and touch—regardless of the types of grafts used. Sensation reappeared as early as three weeks and as late as eleven years after transplantation, and the areas which showed recovery of sensation were about the periphery of the flap at the border of the proximal (central) nerve supply; that is, the recovery of sensation progressed, in the cases studied, from the center to the periphery. The sensation of pain returned first, that of touch next, and the discrimination of temperature last. The authors emphasize the important fact that a regenerating nerve does not follow the Schwann cells of the peripheral nerve, as its fibers in their cases were not parallel to those of the nerves of the transplant.

G. B. HASSIN.

REACTION OF CEREBRAL TISSUE TO DIRECT INJECTION OF OIL. C. R. TUTHILL, and G. M. BECK, Arch. Neurol. & Psychiat. **29**:1263, 1933.

Neuroglial and microglial reactions of the brain have been studied by Tuthill and Beck after the direct introduction of rabbit fat and mineral oil or olive oil into the brains of rabbits. Eleven rabbits were killed at intervals of from twenty-four hours to fifty-one days after the injections of sterile oil into the brain substance. A remarkable phenomenon occurred after the skulls were opened; oil flowed freely from the cerebral surfaces, along the cranial nerves and, on section, from the ventricles. In the meninges macrophages were scarce and, before ten days, very rare; the oligodendroglia were swollen (after twenty-four hours) but did not produce fat granule cells. Astrocytes also exhibited an early reaction—a partial loss of processes near the margin of the wound, where on succeeding days they became hypertrophied, especially in the surrounding nerve tissue. After fifty-one days the injured area was closed by a straight line of hypertrophic astrocytes, while connective tissue fibers in that area were few. Newly formed capillaries were present early—in old wounds from three to five days. Microglia cells were increased, and the capillaries nearest the wound were stripped of microglia twenty-four hours after the injection of oil. The authors emphasize the relation of the microglia to the blood vessels and believe that they have demonstrated transformation of adventitial wall cells into microglia.

G. B. HASSIN.

EFFECTS OF BLOOD LOSS ON ERYTHROID CELLS IN THE RABBIT MARROW. B. F. STEELE, J. Exper. Med. **57**:881, 1933.

The relative proportion of the various sorts of erythroid cells of the bone marrow has been determined after acute and chronic hemorrhage and after damage to the marrow with acetyl-phenylhydrazine. The normal erythroid pattern shows megaloblasts and erythroblasts in the lowest percentage, then normoblasts, reticulocytes and mature erythrocytes, respectively, in increasing proportions. All three states studied show an increasing shift to the left to a condition after

damage by acetyl-phenylhydrazine, in which the erythroblasts and megaloblasts exceed the mature erythrocytes. The marrow pattern finds direct expression in terms of the cells of the blood.

AUTHOR'S SUMMARY.

INCREASE IN GONADOTROPIC EFFECTS OF HYPOPHYSEAL EXTRACTS. H. M. EVANS, M. E. SIMPSON and P. R. AUSTIN, J. Exper. Med. **57**:897, 1933.

The increased gonadotropic effect obtained by combining the follicle-ripening hormone of the anterior pituitary body with hypophyseal extracts can be secured equally well by the use of preparations which contain high amounts of the growth-stimulating or of the gonad-stimulating hormone. In hypophyseal extracts containing the growth hormone, the synergistic effects do not parallel the content of growth-promoting substance. Similarly, in hypophyseal extracts containing the gonad-stimulating hormone, the synergistic effects do not parallel the content in the gonadotropic factor. The hypophyseal substance involved has been prepared sufficiently free of the growth and gonad-stimulating hormones to make it inadmissible to consider either of these substances as responsible for the reaction.

AUTHORS' SUMMARY.

EXPERIMENTAL GRANULOPENIA. E. W. DENNIS, J. Exper. Med. **57**:993, 1933.

Pyogenic organisms, under conditions simulating a focal infection, are capable of producing in rabbits a granulopenia which may cause generalized infection and death. It is suggested that agranulocytosis in man is due to the action of leukocidin, rather than to a specific micro-organism.

AUTHOR'S SUMMARY.

THE SUPRARENAL CORTEX IN SUPRARENAL INSUFFICIENCY IN THE DOG. G. A. HARROP ET AL., J. Exper. Med. **58**:1 and 17, 1933.

The basal oxygen consumption, respiratory quotient, blood flow, blood pressure and the changes in the concentration of the arterial blood were determined in suprarenalectomized dogs (*a*) when they were receiving injections of cortical extract (Swingle-Pfiffner), (*b*) during suprarenal insufficiency induced by withdrawal of the injections and (*c*) during the period of recovery brought about by resumption of the injections of extract. Reasons are advanced for the view that the hemoconcentration which occurs is probably due to loss of fluid through the kidneys, rather than by increased capillary permeability and loss into the tissues, or by loss through the gastro-intestinal tract. The loss of fluid from the plasma and tissues will explain the symptoms which follow withdrawal of injections of the hormone, as well as the fatal outcome. The assumption that the suprarenal cortex or its hormone has a detoxifying action on some product of metabolism is thus rendered unnecessary.

A characteristic alteration in the electrolyte structure of the blood plasma of the suprarenalectomized dog occurs when injections of cortical extract are stopped. This alteration progresses during the course of the suprarenal insufficiency, parallel with the hemoconcentration and the loss in weight. When injections of cortical extract are resumed, the electrolyte structure returns to its original form, the alterations paralleling the dilution of the blood and the return of the body weight to its original level. The hemoconcentration, with the resulting physiologic changes which take place in the suprarenalectomized dog after the cessation of injections of cortical extract, is associated with a loss of sodium and chloride, accompanied by their proper complement of body water, by way of the kidney. Since this effect is produced in the suprarenalectomized animal that is well nourished and in excellent condition solely by the cessation of the injections of the cortical hormone and since the reverse process of repair of the losses of electrolytes and water can be affected solely by resumption of the injection of extract, it follows that all of the observed phenomena are due to this cause, and to this alone. It can be concluded that one function of the cortical extract in the suprarenalectomized dog is that of participa-

tion in the regulation of the sodium and chloride metabolism and, consequently, of the balance and distribution of water. The loss of water, in the absence of the cortical hormone, is sustained partly by the blood plasma, but to a far greater extent by the interstitial body fluid. The available evidence points to the kidney as the locus of this regulatory function of the cortical hormone.

AUTHORS' SUMMARIES.

Pathologic Anatomy

THE PATHOLOGY OF PSITTACOSIS IN MAN. R. D. LILLIE, Nat. Inst. Health, Bull. 161, 1933.

Psittacosis in man is characterized anatomically by a pulmonary inflammatory process which usually goes on to consolidation. Consolidation is primarily focal or lobular, and not especially related to the bronchioles. It often becomes confluent, but even when grossly lobar it shows histologic evidence of its primarily lobular nature. An apparent sequence of congestion and edema, red hepatization, or, better, splenization, and gray hepatization may be observed, but all stages are commonly seen in one case. Histologically, fibrin, red cells, polymorphonuclear leukocytes and epithelial cells appear early in the exudate; fibrin disappears, red corpuscles decrease in number, and leukocytes are replaced by large mononuclear phagocytes and epithelial cells. The alveolar epithelial cells undergo swelling, fatty degeneration and desquamation, with an apparent increase in their numbers, and may be invaded by rickettsiae. In the earliest stages interstitial infiltration is lacking, but a serous exudate soon appears and is later replaced by lymphocytes, large mononuclear cells and occasional tissue mast cells. Necrosis of the septums is sometimes seen. The bronchioles may remain clear, or may contain a serocellular exudate similar to that in the adjacent alveoli. Pleural reaction is relatively infrequent and usually of minor grade. The lymph glands show swelling, vacuolation and phagocytic activity of the sinus endothelium, followed by desquamation and then necrosis of macrophages. The spleen is ordinarily moderately enlarged, soft and congested, and tends to be smaller when gray hepatization of the lung predominates. Histologically, the prominent findings are congestion, infiltration of the pulp by lymphoid cells and an increase in fixed and free phagocytes, sometimes with erythrophagia. In the liver, swelling, vacuolation and phagocytic activity of the Kupffer cells are often found. Focal coagulation necroses of the parenchyma have been found in about a third of the cases, and granulomas, such as have been observed in parrots, were seen in one case. This last case also showed a focal necrosis of the suprarenal cortex. The changes in the heart muscle and kidney are assignable to parenchymatous degeneration, which is usually of moderate grade only. Similarly, Zenker's degeneration and hemorrhages in the body musculature have been reported in a number of cases. Punctate hemorrhages have been seen in the brain substance, in the serous membranes, in the mucosa of the renal pelvis and, rarely, in the subcutaneous tissues. Venous thrombosis has been an occasional complication. This report is based on the published records of autopsies in psittacosis and on nine cases studied histologically by the author, covering a total of fifty-two cases.

AUTHOR'S SUMMARY.

PERFORATION OF THE GASTRO-INTESTINAL TRACT BY BARIUM SULPHATE MEALS. W. HIMMELMANN, München. med. Wchnschr. **79**:1567, 1932.

Thirty-nine cases in which a barium sulphate meal perforated the gastrointestinal tract have been recorded, and the author adds to these one of carcinoma of the stomach, one of chronic peptic ulcer, two of ulcer of the duodenum and one of a strangulated loop of the ileum, in which this accident occurred.

EDWIN F. HIRSCH.

A Case of Parietofrontal Craniopagus. C. Blumensaat, Virchows Arch. f. path. Anat. **285**:140, 1932.

This unusual example of symmetrical double monstrosity, in which the twins were broadly united by their corresponding parietofrontal regions, is of interest because the children lived from February 2 to April 8. During life they exhibited distinct individualities. One had pneumonia and died eight hours before the other. Separation was considered, but roentgen examination revealed that the subdural spaces communicated widely with each other. The two brains were in close apposition, being separated only by pia, the two layers of which were united in places. The brain of the twin who died first revealed histologic evidence of postmortem change.

O. T. Schultz.

Reactions of Lymph Node Groups in Dyscrasias of the Blood. M. Nordmann, Virchows Arch. f. path. Anat. **285**:201, 1932.

In previous studies Nordmann has propounded the thesis that, according to the degree of their normal resorptive functional activity, the lymph node groups may be divided into peripheral (axillary and inguinal), central (celiac and periaortic) and intermediate (cervical and mediastinal). In this paper of seventy-nine pages he seeks to establish his view more thoroughly by presenting a study of the reactions of the various groups of nodes in a variety of dyscrasias of the blood. The material for the study, with the number of cases, was: transfusion, 29 (single, 9; multiple, 8, and experimental in the guinea-pig, 12); agranulocytosis, 6; secondary anemia, 13; pernicious anemia, 3; hemolytic icterus and congenital anasarca of the new-born, 1 each; leukemia, 10 (congenital myeloid, 2; adult myelocytic, 4; adult myeloblastic, 2, and lymphatic, 2). The study consisted in a comparison of similar lymph node groups in the different conditions and study of different groups in each case. In the resorption of blood, especially after transfusion, the lymph nodes act as secondary blood filters, and according to their activity in this respect they may be graded from most active to least active into the following series: celiac, periaortic, mediastinal, cervical, mesenteric, axillary and inguinal. In the various conditions selected for study, the degree of reaction in the various groups in general follows the same sequence. In agranulocytosis, Nordmann recognizes two types of lymphoid reaction, an aplastic and a hyperplastic, depending in part on the age of the subject and in part on the duration of the disease. In this connection it is to be noted that the clinical duration of the final attack of agranulocytosis in the six cases studied varied from six to thirty-two weeks, which is considerably longer than that of the usual case of agranulocytosis. In secondary anemia the lymph nodes are the seat of simple reticular induration or simple lymphoid hyperplasia. Cellular or fibrous sinus catarrh, depending on the duration of the disease, characterizes the nodes of pernicious anemia. Sinus catarrh is defined as a filling of the sinuses by proliferated endothelium and reticulum cells, the proliferative stage being followed by fibrosis. Pernicious anemia is also characterized by moderate myeloid transformation, the degree of which in the various groups follows the usual serial order. The histologic evidence indicates that the myeloid transformation occurs in the sinuses. In the case of hemolytic icterus the nodes revealed both myeloid and erythropoietic transformation, varying in the usual serial sequence in the various groups. The lymphoid tissue was undeveloped in the case of congenital anasarca, and myeloid transformation was not observed. In congenital myeloid leukemia the nodes revealed marked myeloid transformation, which followed the usual sequence in the various groups. The same is true of adult myelocytic leukemia, except that the rule of sequence may be broken and local groups of nodes that are subjected to greater resorptive functioning may present the more extreme grades of myelopoiesis. Myeloblastic leukemia may present a histologic picture like that of lymphatic leukemia. In intermediate forms of myeloid leukemia, the degree of differentiation of the myeloid cells in the various groups follows the usual serial order.

O. T. Schultz.

SENILE CHANGES IN THE INFERIOR VENA CAVA OF BOVINES. C. KRAUSE and X. IWANOFF, Virchows Arch. f. path. Anat. **285**:343, 1932.

In a second study of the vascular lesions of domestic animals the authors examined the inferior vena cava of 300 cattle and 200 domestic buffaloes of different ages. The normal histologic structure of the thoracic portion of the vessel differs from that of the abdominal portion. No changes were noted in the first named portion, but the abdominal portion was uniformly the seat of a senile sclerotic process in animals more than 10 or 12 years old. The process was characterized by fibrosis of the inner portion of the wall with replacement of muscle in this part of the wall by connective tissue. The collagenous tissue of the adventitia was increased, and the adjacent muscle was hypertrophied. Fatty change, necrosis and calcification were not seen except at the mouths of the renal and suprarenal veins, where there occurred changes similar to those caused by the repeated intravenous injection of epinephrine. O. T. SCHULTZ.

UNUSUAL AORTIC LESION IN A NURSLING. K. WOLFF, Virchows Arch. f. path. Anat. **285**:369, 1932.

An infant who died on the twelfth day after birth presented during life the following syndrome: malformation of the right ear, cloudiness of the cornea, cyanosis and a greatly enlarged heart. The antemortem diagnosis was congenital malformation of the heart. The Wassermann reaction of the infant and that of the mother were negative, and gross and histologic examination revealed no evidence of syphilis. At necropsy the heart was found to be enlarged but devoid of developmental errors. In the ascending, transverse and descending portions of the aorta were seen narrow, cleftlike areas that had the appearance of tears. The lesions ceased abruptly just below the diaphragm. Microscopic examination revealed as the earliest lesions poorly defined, irregular areas in the media, in which the elastic fibrils had disappeared. The collagen fibers were swollen and had also in part lost their identity. Muscle tissue was apparently the last element to be altered; the areas contained muscle nuclei in various stages of degeneration. The ground substance had the staining reaction of mucoid degeneration. The surface of the intima was intact over the lesions. Most striking was the absence of any reparative or cellular infiltrative reaction of the tissues in or about the lesions. In the macroscopic tearlike lesions also, reactive phenomena were entirely wanting. The material resulting from the degeneration of the elastic and other tissues of the media had apparently been absorbed, and the intact intima had been folded into the defect thus produced. The small vessels were normal. The lesion described is most like that which Erdheim has described in the aorta of elderly persons as the cause of spontaneous rupture of the aorta, but which has not hitherto been seen in the earlier periods of life. In the case described no cause for the lesion could be found. O. T. SCHULTZ.

PATHOLOGIC HISTOLOGY OF ACUTE ORCHITIS IN MUMPS. C. MANCA, Virchows Arch. f. path. Anat. **285**:426, 1932.

Although the literature includes a few reports of the late stages of orchitis in mumps, it contains, according to the author, no description of the acute stage of this complication. A 21 year old soldier became severely ill with bilateral mumps. On the fourth or fifth day after the onset the left testis became swollen and painful, and a few days later the right testis was involved. Fourteen days after the onset he died of the mumps, necropsy revealing no complicating disease. The earliest stages of the testicular lesion consisted of localized areas of serofibrinous exudation into the intertubular tissue and of leukocytic emigration into the tubules in these areas. Later the areas became confluent, the interstitial tissue became infiltrated by leukocytes, and the walls of the tubules were destroyed. Spermatogenesis had ceased, even where there was no tubular or intertubular inflammatory reaction. The epididymis and vas were free from change. The histologic differ-

ences in the various forms of acute orchitis are discussed. The author believes that the orchitis of mumps can be distinguished histologically from the other forms.

O. T. SCHULTZ.

AN UNUSUAL CASE OF CORPORA AMYLACEA OF THE LUNG. O. SCHILDKNECHT, Virchows Arch. f. path. Anat. **285**:466, 1932.

The case reported differs from previous ones in the large number of bodies present in the lung, in their calcification and in their failure to give any of the reactions for amyloid. The patient was a woman who died at the age of 45 of dementia paralytica. The lungs at necropsy were emphysematous and passively congested. Approximately one fourth of the alveoli contained laminated bodies with the morphology of corpora amylacea. A few of these bodies were present in the interstitial tissue. Many were calcified; this had led to a roentgen diagnosis of miliary tuberculosis during life. The bodies gave the microchemical reaction for iron, but none of the amyloid reactions. The author believes that chronic bronchitis and emphysema had led to the collection of a liquid transudate in the alveoli, desquamated cells being admixed with the fluid. This was followed by transformation of the material into a gel and its precipitation about a central nucleus. The author is unable to give an explanation of the calcification and iron incrustation of the bodies.

O. T. SCHULTZ.

CALCIFICATION AND OSSIFICATION OF THE VERMIFORM APPENDIX. A. KRISPER, Virchows Arch. f. path. Anat. **285**:481, 1932.

The author could find in the literature only two previously reported cases of calcification and ossification of the appendix. He adds four. In three the appendix had been removed surgically and in one the condition was found by chance at autopsy. In one, calcification and ossification were associated with mucocele owing to occlusion of the lumen by a partly necrotic fibrous polyp. In two, histologic examination revealed that tuberculosis was the cause of the calcification; in one of these bone had been formed. The fourth appendix was completely degenerated and calcified, probably as the result of a previous purulent appendicitis.

O. T. SCHULTZ.

THE CAPSULE OF CYSTICERCUS OF THE BRAIN. A. ANTONOW, Virchows Arch. f. path. Anat. **285**:485, 1932.

The structure of the capsule of cysticercus of the brain is dependent on the duration of the infestation. If the duration has been short and the parasite is still alive, the capsule consists of two layers, an inner hyaline membrane and an outer layer of granulation tissue that contains giant cells. After a longer duration and death of the parasite, a third layer of loose connective tissue is laid down internal to the hyaline layer; this layer may contain giant cells. When the dead parasite has been completely broken down, the capsule consists of a single thick layer of dense connective tissue that contains no giant cells. O. T. SCHULTZ.

REACTIONS OF MESOGLIA IN ACUTE NONPURULENT INFECTIONS OF THE CENTRAL NERVOUS SYSTEM. W. K. BELEZKY, Virchows Arch. f. path. Anat. **285**:494, 1932.

In a previous article (*Virchows Arch. f. path. Anat.* **284**:295, 1932) the author presented the evidence that led him to conclude that the mesoglia, consisting of dendritic Hortega cells, oligodendroglia and drainage cells, is of mesodermal origin and corresponds in origin and function to the reticulo-endothelial system of other organs. In acute nonpurulent infections of the central nervous system, such as poliomyelitis, secondary syphilis, spirochetosis and experimental virus diseases, the mesoglia reacts in the same manner as does the reticulo-endothelium of other tissues in these and other nonpurulent infections. The earliest change is swelling

of the oligodendroglia and of the Hortega and drainage cells. Later some of these cells may degenerate and others may proliferate. Proliferation may lead to the formation of focal areas about or near blood vessels, in which cells without processes are transformed into cells with processes; cells of the latter type are derived also from the histiocytes about the blood vessels. Later such areas are transformed into fibrillated glia. The mesoglial reactions are most marked where the action of the infecting agent is most intense, but they tend to be more diffuse than those of the purulent infections of the brain. The reactions are the expression of the protective mechanisms characteristic of reticulo-endothelium wherever it is situated.

O. T. SCHULTZ.

THE SUPRARENAL GLANDS IN TUBERCULOSIS. E. HAUSMANN, Virchows Arch. f. path. Anat. **285**:550, 1932.

Both suprarenals were weighed and examined microscopically in sixty-one cases of tuberculosis. The age of the patients varied from 18 to 52 years. There were no characteristic changes in weight or histologic structure, except the presence of tubercles in three cases and of amyloid in eight; in seven of the latter the amyloid infiltration of the suprarenals was part of general amyloidosis.

O. T. SCHULTZ.

TRANSVERSE RIDGES OF THE INNER SURFACE OF THE BRACHIAL ARTERY. J. LEWIN, Virchows Arch. f. path. Anat. **285**:704, 1932.

Fine transverse ridges on the inner surface of the brachial artery, which is a muscular artery, have been noted by several observers. In elderly persons the ridge may be replaced by a narrow, shallow depression. To determine the incidence and character of the ridges, a systematic study was made of the brachial artery in 141 necropsies. The ages of the subjects varied from 2 months to over 60 years. The ridges were found to be present even at as early an age as 2 years. They increased in number and frequency with increasing age. Microscopic examination showed that they were due to minute transverse tears of the internal elastic lamella, which were healed by connective tissue. Shrinkage of the scar in the later years of life transformed the ridges into depressions. No changes could be detected in the media or intima that would account for the lesions. They are considered physiologic changes associated with age. Mechanical factors may have a part in their formation.

O. T. SCHULTZ.

LOCALIZED IRON AND CALCIUM INCRUSTATION OF THE SPLEEN. W. BRACKERTZ, Virchows Arch. f. path. Anat. **285**:734, 1932.

The spleen that is described by Brackertz was from a woman, aged 23. The clinical diagnosis was cirrhosis of the liver, splenomegaly and possible Banti's disease. The anatomic diagnosis at necropsy was Laënnec's cirrhosis of the liver, chronic splenic tumor and hemochromatosis. In the spleen could be seen a number of small brownish and yellowish nodules. Similar discoloration of the trabecular framework was also noted. Histologically and microchemically these areas had the characteristics of iron and calcium incrustations. The lesions arose in swollen and damaged reticulum fibrils of the pulp and follicles. Such swollen and fragmented fibrils have been described by many authors as mycelia. The calcium deposition is the result of the precipitation of colloidal calcium in a sinus. Fifteen per cent of seventy-six spleens revealed varying degrees of iron and calcium incrustation.

O. T. SCHULTZ.

CHANGES IN PERIPHERAL NERVES AND GANGLIONS IN LARYNGEAL TUBERCULOSIS. A. G. FILATOWA and B. J. LAWREUTJEW, Virchows Arch. f. path. Anat. **286**:1, 1932.

In twenty cases of laryngeal tuberculosis, the superior laryngeal nerve, the cervical portion of the vagus and the ganglion nodosum of the vagus were examined

histologically. In eighteen cases the laryngeal involvement was associated with pulmonary tuberculosis; in three cases, portions of the superior laryngeal nerve that had been resected during life were examined. In the nerves and ganglion cells the authors saw changes that they ascribe to long-continued stimulation and irritation of the nerve structures, resulting in growth of axis cylinders and ganglion cell processes. The growth of the axis cylinder leads to a spiral course and to the formation of lateral branches. The newly formed processes of the ganglion cells may have clubbed ends.

O. T. SCHULTZ.

BILATERAL ABSENCE OF VAS DEFERENS WITHOUT RENAL ANOMALY. A. PRIESEL, Virchows Arch. f. path. Anat. **286**:24, 1932.

Absence of one vas deferens with anomalous development or absence of the kidney or ureter of the same side is not uncommon. Absence of one vas with contralateral renal defect is less common. Absence of the vas on both sides is extremely rare, the only recorded instance being one reported by the author. In this instance there was dystopia of the right kidney with absence of the left kidney and ureter. Only two cases of unilateral absence of the vas with a normal kidney and ureter on each side have been reported. In the present report the author describes, as the only instance on record, a case of bilateral absence of the vas with a normal urinary system on each side. The man died at the age of 47 of atherosclerosis. The external configuration of the body was of the male type. The testes were large and were in the scrotum. Spermatogenesis was active. The head of the epididymis was present on each side; its tubules were distended by the degenerated products of spermatogenesis. The body and tail of the epididymis, the vas, the seminal vesicle and the ejaculatory duct of each side were absent. The prostate and Cowper's glands were normal.

O. T. SCHULTZ.

A CASE OF PAPILLARY HYPERKERATOSIS OF WALDEYER'S TONSILLAR RING. G. GERSTEL, Virchows Arch. f. path. Anat. **286**:116, 1932.

The unusual condition reported was first described in 1873 by B. Fränkel under the name benign lingual and tonsillar mycosis. Death was due to pulmonary tuberculosis in Gerstel's case. On the base of the tongue and in the pharynx, in the region of the lingual, faucial and pharyngeal tonsils that make up Waldeyer's ring, were numerous elevated, rounded and thornlike hyperkeratoses. These arose from the squamous epithelium of the crypts of the lymphoid tissue. The author disagrees with the view of some observers that the condition is a mycosis. No fungi could be seen in the lesions, and the bacteria present were held to be secondary invaders. The process is not inflammatory. It is an epithelial hyperplasia that is sharply limited to the crypts of lymphoid tissue, where multiple localized areas of leukoplakia most often occur.

O. T. SCHULTZ.

MYCOSIS FUNGOIDES WITH INVOLVEMENT OF THE BRAIN AND CRANIAL NERVES. C. MONCORPS and G. BORGER, Virchows Arch. f. path. Anat. **286**:157, 1932.

Six and one-half months before his hospitalization lesions of mycosis fungoides appeared on the trunk of a man, aged 35. Five months later the general condition was poor and neurologic symptoms occurred. In the further course of the disease there developed symptoms referable to involvement of practically all of the cranial nerves and others indicative of increased intracranial pressure. Histologic examination at necropsy revealed the presence of infiltrating cellular tissue, similar to that of the cutaneous lesions, in the pia, in the region of the corpora quadrigemina and left caudate nucleus, in both gasserian ganglions and in all the cranial nerves. The degree of involvement of the testis was out of proportion to the clinical and gross anatomic findings.

O. T. SCHULTZ.

CRITICAL SUMMARY OF THE PATHOLOGIC HISTOLOGY OF RHEUMATIC INFECTION. F. KLINGE, Virchows Arch. f. path. Anat. **286**:344, 1932.

In this paper, the twelfth of a series of contributions by Klinge and his associates, Klinge presents a critical summary of the pathologic histology of rheumatic infection. He first states his concept of the disease. It begins as a primary infection of the upper air passages. If the pharyngeal catarrh does not heal within a few days, rheumatic fever results. This disease, in which multiple lesions occur in the various tissues and organs of the body, may manifest itself clinically as rheumatic polyarthritis, as visceral rheumatism or as peripheral rheumatism. After persisting for a number of weeks, the disease may heal, with a variable amount of permanent damage, or it may become chronic. In the chronic stage, which may be articular, visceral or combined, the lesions of the acute stage become cicatrized and new lesions develop. After a variable period of chronicity the disease may heal, usually with considerable permanent damage, or it may become transformed into chronic sepsis. In his summary of the pathologic histology of the disease, Klinge describes the lesions of the various stages and forms of the disease in the various organs or organ systems under the following headings: heart (valves, myocardium, pericardium); blood vessels; tonsils and organs of the neck; joints (synovial membrane; subsynovial, capsular and periarticular connective tissue); skin (nodose rheumatism, erythema multiforme and nodosum); bursae and tendons; musculature; nerves; lungs; liver; spleen; lymph nodes, and kidneys. In whatever organs the lesions may be situated, they begin as focal areas of edema and fibrinoid swelling and degeneration of the ground substance of collagenous connective tissue; the fibrils are not destroyed in the process. To this degenerative process there are added hypertrophy and proliferation of connective tissue cells and lymphocytic and leukocytic infiltration. When the lesions occur in smooth or striped muscle, necrosis of muscle fibers results. In its essential details the rheumatic lesion does not differ from lesions that may be caused by bacteria that do not incite suppuration. The rheumatic process differs from other infectious inflammatory processes in the multiplicity of its lesions, in their widespread distribution throughout the tissues and organs of the body and in the limitation of the early, focal, fibrinoid degenerative process to the connective tissues. The article of forty-five pages has twenty-five illustrations, some of which are in color.

O. T. SCHULTZ.

ACUTE NEPHRITIS AND CORTICAL NECROSIS FOLLOWING SEPTIC ABORTION. B. ZU JEDDELOH, Virchows Arch. f. path. Anat. **286**:389, 1932.

Criminal abortion during the third and the fourth month of pregnancy in two women aged 38 and 19 respectively was followed by sepsis, with acute general peritonitis in one case. Anuria developed and led to death. In each case the kidneys revealed the presence of an intense acute inflammatory process, involving especially the glomeruli, and widespread necrosis of the cortex. The glomerular vessels and the small arterioles were thrombosed. The condition differed from the cortical renal necrosis that occurs usually in the later months of pregnancy in the greater degree of inflammatory reaction. After a discussion of the relation of cortical necrosis to eclampsia, the author concludes that infection was the chief underlying factor in his cases, but that it acted on kidneys susceptible to or already injured by eclamptic intoxication.

O. T. SCHULTZ.

AMYLOIDOSIS IN A NURSLING. I. OBERG, Virchows Arch. f. path. Anat. **286**:476, 1932.

Amyloidosis is rare in infancy. With the exception of one doubtful case in a child aged 1½ years, the author could find no reference to the occurrence of the condition in children under 4 years of age. The case reported was that of a child, aged 2½ months, who died of pneumococcic meningitis secondary to bilateral otitis media. The gross appearance of the spleen led to an anatomic diagnosis of amyloid disease. The splenic pulp and the glomeruli of the kidney on

microscopic examination contained protein material with the optical and physical properties and the localization of amyloid. The material did not give the characteristic microchemical reactions of amyloid. O. T. SCHULTZ.

AMYLOIDOSIS AND RETICULO-ENDOTHELIAL REACTIONS IN HORSES USED FOR PRODUCTION OF SERUM. ERNA DOERKEN, Virchows Arch. f. path. Anat. **286**:487, 1932.

The tissues of horses that have been used in the production of antitoxic and antibacterial serums offer a material for the study of reticulo-endothelial reactions in immunity. Amyloidosis is said to be frequent and is considered by veterinarians to be the most common cause of death of the animals. Material from one hundred serum horses formed the basis of the study reported. The animals had been used for the production of serum for from two and one-half to fifty-four months. The horses had been used for the production of a variety of antiserums, but the largest number had been used in the preparation of diphtheria and tetanus antitoxins (forty-four and twenty-six, respectively). Amyloidosis was observed in sixty. The percentages of its incidence distribution in the various organs were as follows: spleen, 100; liver, 44; suprarenals, 34; kidneys, 21, and intestines, 12. In eight animals amyloid infiltration led to rupture of the liver and death. Amyloidosis was relatively more frequent in horses used for scarlet fever antiserum than in those used for other antiserums. Reticulo-endothelial reactions, which were present in every animal, were of three types: diffuse hypertrophy and hyperplasia, small granulomatous foci and true granulomas. It was not possible to determine any relation between these types of reaction and the duration of immunization or the kind of serum prepared. Reticulo-endothelial reactions and amyloid infiltration appeared to have a close relationship. The cellular reaction occurred first and was necessary for the production of amyloidosis. O. T. SCHULTZ.

Microbiology and Parasitology

CERVICO-VAGINITIS OF GONOCOCCAL ORIGIN IN CHILDREN. W. M. BRUNET, D. M. TOLLE, S. A. SCUDDER and A. R. MECALF, Hosp. Soc. Ser. Mag., supp. 1, 1933.

A series of 322 young children with vaginitis of supposed gonococcal origin were studied, 244 with relative completeness. It was found that cervicovaginitis in children does not differ widely from the similar infection in adults. The difference from the adult picture lies in the rarity of inflammation of the vulvovaginal glands, of the urethra, of the fallopian tubes and of the peritoneum. Pelvic involvement occurred in only four cases, and infection of the eye in but two, only one of which was gonorrheal. Rectal involvement was rare, and no case of arthritis was observed. Examination of the cervix showed it to be involved in four fifths of the cases, and there was a strong tendency to persistence. Only three cases of the series showed gram-negative diplococci other than gonococci. A differential stain which incorporates the combined features of the original Gram and Pappenheim methods was found to be reliable for the diagnosis of gonorrheal infection. Cultures constituted the most important method of checking up on cases of cervicovaginitis. Fresh rabbit serum, applied at the site of probable primary infection, acted as a provocative in chronic cases in which cultures had become negative. LUKE W. HUNT.

KENDALL'S MEDIUM. H. M. CARPENTER and P. H. LONG, J. Bact. **25**:241, 1933.

Although Kendall's technic was followed minutely, filtrable forms of Bacillus typhosus and beta hemolytic streptococci were not produced. It was not possible to cultivate staphylococci from staphylococcus bacteriophage, nor a filtrable coccus from "cold" virus. Diphtheroids and B. subtilis were cultivated occasionally from commercial vaccine virus, but in view of the well known observation that these organisms may be contaminants of vaccine virus, no importance was attached to these results. AUTHORS' SUMMARY.

PNEUMOCOCCUS VARIANTS INTERMEDIATE BETWEEN THE S AND R FORMS. F. G. BLAKE and J. D. TRASK, J. Bact. **25**:289, 1933.

Five intermediate variants between type I-S and type I-R pneumococcus have been detected by growing type I-S pneumococci in homologous immune serum broth. They progressively appear and disappear in serial cultures. Two of these, I-b and I-c, were easily stabilized in pure culture. The intermediates between S and R show a progressive and orderly change in their agglutination reactions in homologous and heterologous immune serums. They also show a progressive loss in virulence for white mice. Only one intermediate, II-c, has been derived from type II-S. It was easily stabilized and is comparable to I-c in its agglutination reactions and virulence. The observations described indicate that the dissociation of S pneumococci by growth in homologous immune serum is not a simple S → R change but that a considerable number of intermediate variants with fairly well defined characteristics appear and disappear during the process.

AUTHORS' SUMMARY.

THE HISTOLOGICAL CHANGES AND THE FATE OF TUBERCLE BACILLI IN REINFECTED RABBITS. M. B. LURIE, J. Exper. Med. **57**:181, 1933.

Immunity to reinfection is a function of the increased capacity of the mononuclear phagocytes to destroy tubercle bacilli and varies directly with the extent of the primary lesion; however, it is rarely sufficient to annihilate completely the micro-organism. This acquired immunity is superimposed on the natural resistance of a given organ. In the presence of sufficient immunity, such as occurs with the persistence of an extensive primary lesion, small numbers of tubercle bacilli are destroyed by the mononuclear cells in situ without local or general infiltration of the tissues by polymorphonuclear or mononuclear leukocytes. Larger numbers of bacilli are destroyed within twenty-four hours by an accelerated formation of sharply localized nodules of mononuclear phagocytes. These progress no further and are absorbed or result in inconspicuous microscopic collections of epithelioid and giant cells. In the presence of less immunity, such as occurs when the primary lesion has almost completely healed, the immediate inflammatory reaction is more intense and diffuse and persists longer. It results in a less rapid disappearance of the bacilli and in a more extensive formation of tubercles. These appear much earlier than in the normal animal and soon resolve. Tubercle bacilli of reinfection may be destroyed even though the primary lesion in the lung and kidney is progressive. This is due to an unhindered extracellular multiplication of the bacilli in the caseous foci that undergo softening and excavation. Resistance may be overwhelmed by the spread of tremendous numbers of living bacilli from these foci through the bronchi or renal tubules, while the moderate numbers of reinfecting bacilli reaching the organs by way of the blood stream are destroyed.

AUTHOR'S SUMMARY.

SPONTANEOUS CONJUNCTIVAL FOLLICULOSIS OF MONKEYS. P. K. OLITSKY and J. R. TYLER, J. Exper. Med. **57**:229, 1933.

Spontaneous folliculosis of Macacus rhesus monkeys, a type of follicular conjunctivitis associated with marked, local, inflammatory reactions, is apparently a disease sui generis, due to a specific infectious agent. It can be transmitted from monkey to monkey by means of subconjunctival injection of suspensions, and by conjunctival swabbing of the secretions, of affected tissues, or by contact of normal animals with monkeys with folliculosis. The agent causing folliculosis has failed in our hands to pass through Berkefeld and Seitz filters, even those of an unusual degree of permeability; and the lesions that it causes show no cellular inclusions suggestive of the action of a virus. The condition is due apparently

to an organism of low grade pathogenicity. The essential histopathologic structure corresponds to that of a folliculoma which, while not identical with a granuloma, bears certain resemblances to the latter. The studies here reported concern only one species of monkey, Macacus rhesus. Further investigations will be carried out on different species of Anthropoidea and other animals.

AUTHORS' SUMMARY.

EXPERIMENTAL AVIAN TUBERCULOSIS PRODUCED BY DISSOCIATED VARIANTS OF TUBERCLE BACILLI. W. A. WINN and S. A. PETROFF, J. Exper. Med. **57**:239, 1933.

Four variants, S, F.S., R and Ch, dissociated from an avian tubercle bacillus, A, have been described. They have different physical and chemical properties. The leukocytic response in S and F.S. is of acute type, while that produced by R and Ch variants is indicative of a chronic, healing tuberculosis. The tubercle formed by S is of an acute, "toxic" type; the F.S. more of a foreign body type, and that of R and Ch, relatively benign. The S variant is by far the most virulent and is closely followed by the F.S. type. The R and Ch variants are comparatively avirulent.

AUTHORS' SUMMARY.

TRANSFORMATION OF TYPE IN VITRO BY PNEUMOCOCCUS EXTRACTS. J. L. ALLOWAY, J. Exper. Med. **57**:265, 1933.

Pneumococcus extracts highly active in inducing the in vitro transformation of the specific types of pneumococcus have been prepared by dissolving S cells with sodium desoxycholate, precipitating the dissolved material in alcohol in which the bile salt remains soluble and extracting the precipitate in salt solution. Further purification of these active extracts has been attained by the removal of considerable inactive material by charcoal adsorption and by reprecipitation of the adsorbed extract in alcohol or acetone. The importance of using young cultures for extraction, and of preventing autolysis during the preparation of the extracts, is emphasized. Extracts prepared by the method described have been filtered through Berkefeld candles (V, N and W) without appreciable loss in activity, provided the reaction of the extract was slightly alkaline at the time of filtration. The purified and filtered extracts are waterclear and sterile by rigid cultural and animal tests. They have been heated to temperatures of 60 C. for thirty minutes without appreciable loss in their capacity to induce specific changes in type. And although they have generally shown definite decrease in potency after heating to temperatures above 80 C., some extracts have been found active even after an exposure of ten minutes to a temperature of 90 C. They have been completely inactivated by boiling. Relatively small amounts of extract have been effective when added to a broth medium containing normal serum or serous fluid. In this medium, R pneumococci, irrespective of their type derivation, have developed and thereafter retained all the type-specific characteristics of the encapsulated S cells from which the extract was prepared. The specific action of the extracts is discussed with reference to their transforming and antigenic properties.

AUTHOR'S SUMMARY.

CHANGES IN BACTERIUM COLI AND BACILLUS MEGATHERIUM UNDER THE INFLUENCE OF BACTERIOPHAGE. S. BAYNE-JONES and L. A. SANDHOLZER, J. Exper. Med. **57**:279, 1933.

Enlargement or swelling of the cells of Bacterium coli usually, but not always, precedes lysis. Some of the enlargement is an expression of increase of cell substance and is not altogether due to imbibition of water. Cells of early generations of Bact. coli enlarge to greater absolute and relative proportions than cells of later generations. Enlargement does not occur before lysis in Bacillus megatherium. The terminal stage of lysis of Bact. coli is explosive, occupying from one-half to seventh-eighths second. The terminal stage of lysis of B. megatherium

is a slow disintegrative process, extending over two to ten minutes. Bacteriophage inhibits fission of some cells, but does not stop the reproduction of other cells in contact with it. The genealogical records of six generations of cells of Bact. coli and of two generations of cells of B. megatherium indicate that bacteriophage may be transmitted through parents to the offspring which ultimately undergo lysis. Bacteriophage spreads by contact through a group of cells and also along paths determined by genetical relationships. A large amount of cellular débris remains after the lysis of the cells in both of these species of bacteria. This residue of material is in the form of irregularly shaped masses and granules. This material is not in solution at the time of lysis and appears not to be digested or hydrolyzed. Theories of the mechanism of lysis are discussed. It is suggested that reduction of surface tension of the cells may be an important factor in the mechanism of lysis.

AUTHORS' SUMMARY.

A STUDY OF THE BACTERIAL CAPSULE BY NEW METHODS. J. W. CHURCHMAN and N. V. EMELIANOFF, J. Exper. Med. **57**:485, 1933.

"Whatever the nature of the structures we have described we do not wish to be understood as suggesting that bacterial capsules necessarily resemble each other in any way. That they differ in chemical and biological properties appears certain. It is also known that they differ in the same organism under varying circumstances (e. g., the change produced in the capsule of D. pneumoniae III S by injection into the peritoneum of the mouse). It is to be expected that they will be found to differ in physical characteristics. The evidence we have presented should, we think, only be interpreted as justifying a reexamination of the whole question in which the problems raised will be attacked by means of methods not subject to some of the limitations of tinctorial technic. Such studies we now have under way."

MENINGOCOCCUS INFECTION. G. RAKE, J. Exper. Med. **57**:549 and 561, 1933.

Freshly isolated strains of meningococci present a number of characteristics which can be shown to differ not inconsiderably from those of stock strains long maintained on artificial mediums. Rough variants of the different types can be demonstrated, either arising spontaneously in vivo or in vitro, or evoked in the laboratory by the method described by Enders. Neither the freshly isolated strains —which are smooth—nor, in most cases, the rough variants of them are stable, both showing a tendency to pass over into the stock form or variant. The stock strains in the course of transformation from the freshly isolated strains show changes in morphology and cultural characteristics, and in viability in defibrinated blood.

The production of monovalent serums for agglutinin or precipitin reactions with freshly isolated strains of meningococci is described. Agglutination reactions with such serums can be carried out more rapidly, at lower temperatures and in lower dilutions, than with the standard monovalent serums prepared from stock cultures, while the results so obtained are more satisfactory owing to the relative absence of cross-agglutination.

AUTHOR'S SUMMARY.

THE CULTIVATION OF VACCINE VIRUS IN LIFELESS MEDIA. T. M. RIVERS and S. M. WARD, J. Exper. Med. **57**:741, 1933.

We have made ten attempts to cultivate vaccine virus in tissue extracts prepared according to the method described by Eagles and Kordi. Renal, testicular and chick embryo extracts were employed with a dermal strain of vaccine virus and with the Levaditi strain of neurovaccine virus. In no instance were we able to show that the virus multiplied in the extract mediums. Both of these strains of virus, however, multiplied in mediums containing bits of minced viable tissue. Furthermore, treatment of rabbit testicular tissue and chick embryo tissue in the manner described by Eagles and Kordi for the preparation of the extracts leaves some cells not only alive but capable of proliferation. Although the results of

our work are not in accord with those obtained by Eagles and Kordi, we offer no explanation for the discrepancy. Nevertheless, one cannot examine the results of our work recorded in the six tables without recognizing the fact that in the types of mediums used the presence of viable cells appears to be essential for the multiplication of vaccine virus. Rabbit testicular tissue and bits of chick embryos support the regeneration of the active agent more efficiently than does rabbit renal tissue.

AUTHORS' SUMMARY.

THE ETIOLOGY OF SPONTANEOUS CONJUNCTIVAL FOLLICULOSIS OF MONKEYS. P. K. OLITSKY, J. T. SYVERTON and J. R. TYLER, J. Exper. Med. **57**:871, 1933.

In the bacteriologic study here reported, we undertook an investigation of the flora associated with spontaneous conjunctival folliculosis. Following the plan of Noguchi, monkeys and chimpanzees were inoculated with the different organisms recovered from affected tissues. By this means, we disclosed among the bacteria a new species, Bacterium simiae, which was found to be specifically active, in that it induced follicular reactions in the conjunctiva apparently indistinguishable from the disease as it occurs in nature. The specific action of the bacterium in animals is the more striking when it is compared with the innocuousness of other organisms isolated from cases of folliculosis, and also when considered in relation to the behavior of quarantined animals. While the disease arises spontaneously in stock animals, of over three hundred normal rhesus monkeys—these being isolated in lots of from ten to twenty and quarantined from six to fourteen weeks—not one has as yet shown folliculosis. With the significant exception already mentioned, the experimental disease was produced only when the inoculum contained either folliculosis tissue or cultures of the simian organism. Apart from these observations, the experimental results indicate that the bacterium has thus far been recovered only from cases of folliculosis and not from other forms of conjunctivitis or from normal tissues; the micro-organism has been isolated not only from affected conjunctivae of stock monkeys but also from the tissue of animals—macaques and apes—experimentally infected with the bacterium, and such recovered cultures have, in turn, been found to be specifically pathogenic in normal rhesus monkeys and chimpanzees. We may therefore postulate from this experimental study that an intimate relation exists between Bacterium simiae and spontaneous conjunctival folliculosis of simians.

AUTHORS' SUMMARY.

THE REACTION OF RABBITS TO SYPHILIS. P. D. ROSAHN, J. Exper. Med. **57**:907, 1933.

The results reported indicate that breed, race or family is a factor which significantly influences the response to infection with Spirochaeta pallida.

PATHOGENICITY OF PSEUDORABIES VIRUS ON ANIMAL PASSAGE. R. E. SHOPE, J. Exper. Med. **57**:925, 1933.

Pseudorabies virus, Iowa strain ("mad itch"), after passage through the brain of a guinea-pig, fails to produce infection in guinea-pigs when injected subcutaneously unless enormous doses are employed. Such virus is still pathogenic for rabbits when given subcutaneously and for rabbits and guinea-pigs intracerebrally. Comparison of the amounts of virus present in the brains of rabbits and guinea-pigs following fatal cerebral infection shows that the latter contain, per gram, only approximately one-tenth the amount of virus in the former. Comparing the resistance of the two species to subcutaneously administered pseudorabies virus, it has been found that rabbits are approximately one hundred times more susceptible than guinea-pigs. Over and above the working of these two factors, passage through the guinea-pig appears to achieve some actual attenuation of virus when tested by subcutaneous inoculation into guinea-pigs.

AUTHOR'S SUMMARY.

LOCALIZATIONS OF POLIOMYELITIS VIRUS IN CENTRAL NERVOUS SYSTEM. H. K. FABER and L. P. GEBHARDT, J. Exper. Med. **57**:933, 1933.

About four days after intranasal instillation, the virus of poliomyelitis establishes its initial focus, within the central nervous system, in the olfactory bulbs. It apparently reaches this structure through the axons of the olfactory nerves after primarily infecting the olfactory cells of the nasal mucosa. From this initial focus, the virus spreads (on the fifth and sixth days) through the olfactory tracts and their connections in the brain stem. A secondary focus in the hypothalamus is first established. From this, two main channels can be discerned: first, to the medulla; second, to the thalamus and midbrain. On the seventh day, the virus can first be detected in the spinal cord. It is widespread but is found in larger amounts in the cervical than in the lumbar segments. It is present in both the anterior and posterior horns, either in equal amounts or in slightly larger amounts in the posterior horn. It is also present in the intervertebral ganglions. The surmise is presented that the main route of infection of the cord is not from the medulla (which had been infected as early as the fifth day) but along the sensory tracts, presumably from the thalamus (spinothalamic tracts). Certain portions of the central nervous system were never found to contain demonstrable quantities of virus: These were the cortex of the frontal and parietal lobes (neopallium), and the cerebellum. The olfactory (archipallial) cortex (hippocampus) was only once found to contain virus; this occurred on the seventh day and in small amounts, and presumably had its source in the olfactory bulbs. The experiments of the seventh day suggest that virus had died out in areas previously infected (in the hypothalamus and thalamus, particularly), while continuing, apparently undiminished, in the midbrain and medulla, and spreading to the cord. These observations are in harmony with the general contentions of Fairbrother and Hurst that the virus is better adapted to survival in the lower portions of the cerebrospinal axis than in the higher. The conception here presented of the manner of entrance and routes of propagation of the virus of poliomyelitis in the experimental animal appears to be in essential agreement with the clinical and pathologic characteristics of the disease in man. Both the experimental disease and the disease as it occurs in man appear to present the features of an infection spread through nerve tissue only. It is unnecessary to assume that at any stage of its progress, during the incubation period or later, systemic or general extranervous infection is present.

AUTHORS' SUMMARY.

BACTERIAL INVASION FROM AREAS OF INFLAMMATION. V. MENKIN, J. Exper. Med. **57**:977, 1933.

Trypan blue injected into an area of cutaneous inflammation induced by Staphylococcus aureus failed to drain readily to the tributary lymphatics when the dye was injected as early as one hour after the inoculation of the microorganisms. Trypan blue introduced into an area of cutaneous inflammation induced by pneumococcus type I was retained in situ when the dye was injected about six or more hours after the inoculation of the bacteria. When an area of cutaneous inflammation was induced by the inoculation of a culture of Streptococcus haemolyticus, trypan blue injected into it drained readily to the tributary lymphatics for the first thirty hours following the onset of the inflammatory reaction. When the inflammation had lasted for forty-five hours or longer, the dye was fixed in situ and failed in most instances to reach readily the tributary lymphatics. The rapidity of fixation of the dye in the instances given would appear to depend on mechanical obstruction in the form of both a fibrinous network and thrombosed lymphatics or thrombosed lymphatics alone at the site of inflammation. As staphylococci, pneumococci and streptococci spread from the site of cutaneous inoculation primarily through lymphatic channels, the difference in the rapidity with which mechanical obstruction is set up in the areas inflamed by them will help to explain the differing invasive abilities of these pyogenic organisms.

AUTHOR'S SUMMARY.

ACUTE ENCEPHALOMYELITIS IN MONKEYS. T. M. RIVERS, D. H. SPRUNT and G. P. BERRY, J. Exper. Med. **58**:39, 1933.

No evidence was found to support the idea that vaccine virus placed in the cisterna magna is capable of producing an acute disseminated encephalomyelitis with perivascular demyelination either in normal or in partially immune monkeys. A testicular extract (Reynals' factor) did not induce vaccine virus to cause an acute disseminated encephalomyelitis in monkeys. Repeated intramuscular injections of brain extracts and brain emulsions into eight monkeys were followed in two instances by an inflammatory reaction, accompanied by demyelination, in the central nervous system. The exact relation of the injections to the disease of the nervous system is not clear. The combined action of vaccine virus and an emulsion of fresh rabbit brain did not lead to the production of an acute disseminated encephalomyelitis in monkeys that had received repeated intramuscular injections of emulsions and alcohol-ether extracts of normal rabbit brains.

AUTHORS' SUMMARY.

INFLUENZAL MENINGITIS. L. D. FOTHERGILL and J. WRIGHT, J. Immunol. **24**:273, 1933.

Influenzal meningitis is rarely seen in children under 2 months of age or beyond 6 years of age. About 80 per cent of the cases occur between the ages of 2 months and 3 years. Cord blood and the blood of infants under 2 months of age have considerable bactericidal power. With rare exceptions the blood of children between the ages of 2 months and 3 years has practically no bactericidal power. After 3 years, the bactericidal power gradually rises and appears to be permanent in adult life.

AUTHORS' SUMMARY.

INHERITANCE AS A FACTOR IN RESISTANCE TO AN INFECTIOUS DISEASE. M. R. IRWIN, J. Immunol. **24**:285, 297, 313, 319, 329 and 343, 1933.

1. A specific dose of a strain of Salmonella enteritidis injected intraperitoneally into members of an inbred strain of rats over a four year period produced a mortality of 93.5 per cent. The slight discrepancy from the reaction of an ideal control stock could not be explained on the basis of seasonal effects, environmental changes or by any measurable physical differences in the animals.

2. Selection within a random-mated stock of rats has been effective in isolating lines which continually produced an appreciable increase in the number of subjects resistant to a specific dose of a strain of S. enteritidis over the number that were found in the nonselected parental population. Considerable variation was noted among the survivors in their ability to transmit resistance to their offspring. The hybrid progeny from matings between survivors and members of a susceptible inbred race showed a greater resemblance in mortality to that of their resistant parents than to that of the susceptible parental strain. Offspring from matings of hybrid survivors to members of the susceptible strain, and inter se, gave further evidence that hereditary factors were in a large part responsible for the resistance displayed in the selected stocks. The genetic factors operative in the experiments were seemingly multiple, presumably cumulative in effect, and some were at least partially dominant over those making for susceptibility.

3. In an analysis of the reaction of a population to an infection, it is of the utmost value to determine whether or not the average is typical of the set. Should a critical examination reveal that the underlying probability for the event is not common for all of the subdivisions, but instead varies from subset to subset, it is reasonable to conclude that the causes of the deviations from the normal distribution lies within the subsets themselves. In such a case the average should be used simply as an explanatory figure, and not as representative of the set as a whole. Granting a reasonable degree of control of the environmental factors in these experiments, and also that there was uniformity in behavior between successive progenies of particular matings, the most reasonable conclusion would be to attribute

the differences in mortality between the subsets in large part to hereditary factors. Examples given in this article, combined with others previously reported, show clearly the variation one may anticipate between survivors in their ability to pass on factors for resistance to their offspring. Also, data have been given which set forth the variation in mortality which may be encountered in the progeny from a single male mated with various females.

4. Genetic and immunologic tests gave no indication of an influence of passive immunity in the experiments. The progeny from either carrier or noncarrier parents tended to be resistant only if so determined by their line of descent. There was no difference in the proportions of carriers within the surviving litters of carrier or noncarrier parents.

5. The weight in itself of the host animals cannot be considered as having contributed more than a minor part in the differences in mortality between the strains. The stock of the latest average weight at injection showed the greatest proportionate number of resistant animals. The determinative influence of the weight on the variation in mortality within the various strains was variable, with a tendency in each for a lower mortality to be associated with the litters of greater weight.

6. (With T. P. Hughes.) The whole blood of rats from two inbred strains highly susceptible to infection with Salmonella enteritidis showed little or no bactericidal activity toward this organism. Those subjects whose blood showed varying degrees of bactericidal activity were, on experimental infection, approximately equally distributed in surviving and nonsurviving groups.

AUTHOR'S SUMMARIES.

SEROLOGIC AND CULTURAL STUDIES OF MENINGOCOCCI, WITH SPECIAL REFERENCE TO TYPE V. B. E. SEGAL, J. Infect. Dis. **52**:1, 1933.

Of the hundred strains of meningococci studied, thirty-six strains by agglutination and absorption tests were found to be type I, ten strains type II, twenty type III and twelve type IV. An indirect method of classification was resorted to in five cases. Rabbits were immunized with each of the strains, and the agglutination and absorption reactions of the homologous antiserums were studied. Four were found to be of type IV and one of type III. Seventeen strains were found to differ serologically from any of the known types of meningococci. They have been shown to form a separate group distinguishable from the Gordon type strains by their agglutination and absorption reactions. The cultural and biochemical reactions of these seventeen strains I do not consider as sufficiently distinct to warrant their being placed apart as a new species. A fifth type is proposed for this group of seventeen strains, since the four existing Gordon types are differentiated purely on the basis of serologic differences. The seventeen strains forming a fifth type of meningococcus were all isolated from the spinal fluids in cases of clinical cerebrospinal meningitis occurring in the Chicago epidemic of 1928, in which all the four known Gordon types were encountered.

AUTHOR'S SUMMARY.

RELATION OF GASTRO-INTESTINAL POISON TO OTHER TOXIC SUBSTANCES PRODUCED BY STAPHYLOCOCCI. O. C. WOOLPERT and G. M. DACK, J. Infect. Dis. **52**:6, 1933.

The method of the production of staphylococcic toxin on semisolid medium under partial carbon dioxide atmosphere has been applied to several strains of Staphylococcus aureus from food poisoning and other sources. By this method it has been possible to prepare powerful staphylococcic gastro-intestinal poisons which when fed to rhesus monkeys consistently caused symptoms of food poisoning similar to those seen in man. This enterotoxic substance appears to be distinct from the hemolysin, dermotoxin and killing toxin found in such preparations. Two strains studied produced all of these toxins; one produced none and one strain

yielded no gastro-intestinal poison but large amounts of the other toxins mentioned. The gastro-intestinal poison was more resistant to heating and to adsorption than the other toxins, and was not neutralized by antiserum effective against the others. However, in no case was this food poison produced without the production of these other toxins, and whenever food poison was formed there seemed to be a rough correlation between the amount of food poison and the amount of these other toxins. The rhesus monkey was readily immunized actively against the effects of this poison, but attempts at passive immunization failed. In the use of the methods employed herein, a basis is afforded for the laboratory study of staphylococcic food poison.

AUTHORS' SUMMARY.

COLONY FORMATION OF DIPLOCOCCUS RUBEOLAE (MEASLES). R. TUNNICLIFF, J. Infect. Dis. **52**:39, 1933.

The strains of green-producing Diplococcus rubeolae isolated before and during the eruptive stage of measles have been found to belong to one immunologic group (opsonic test) and to produce a small, conical, depressed colony developing often into a hard, lobulated, adherent colony. The diplococci from the depressed conical colony were virulent for mice and produced an exanthem in rabbits. A variety of other greening colonies was also observed in the acute stage and during convalescence in measles, but opsonically their cocci did not belong to the measles group. Smooth convex, smooth conical and lacy-edged rough colonies, as well as minute G colonies, have been dissociated from colonies of D. rubeolae. The G type of colony was observed both before and after filtration through a Berkefeld V filter, but so far has not been recovered from Berkefeld N filters. Anhemolytic diplococci later producing greening have been recovered from Berkefeld N filtrates of D. rubeolae by serial plate cultures. So far neither the cocci from smooth and rough colonies dissociated from D. rubeolae nor those recovered from its N Berkefeld filtrates have been reverted immunologically or colonially to the depressed conical colony of D. rubeolae.

AUTHOR'S SUMMARY.

EXPERIMENTAL INFECTION OF MAN WITH A BOVINE STRAIN OF BRUCELLA ABORTUS. P. MORALES-OTERO, J. Infect. Dis. **52**:54, 1933.

A family consisting of three members volunteered to ingest for six weeks the infected milk of a cow suffering from infection with Brucella abortus. At the end of this period, none of the members had at any time shown any symptoms of the disease, and their blood cultures and blood agglutination tests remained persistently negative for Br. abortus. Two other volunteers inoculated, one through normal and the other through abraded skin, with the strain isolated from the infected cow's milk presented no symptoms of the disease, and their blood cultures were persistently negative for Br. abortus. In the blood of the latter of the two persons, a transitory positive agglutination of the organism (in a 1:40 dilution) was observed during the third and fourth weeks of the experiment.

AUTHOR'S SUMMARY.

A MEDIUM FOR THE ISOLATION OF BACILLUS PERTUSSIS. J. H. BAILEY, J. Infect. Dis. **52**:94, 1933.

A modification of the original Bordet-Gengou medium for the isolation and cultivation of Bacillus pertussis is given, consisting of the substitution of potato starch or potato flour for a portion of the potato in the original medium. The starch medium possesses the following advantages over the original medium: Batches are easily duplicated; it is easier to prepare, and B. pertussis appears in less time than on the original medium. The cultural characteristics of B. pertussis are the same on the starch medium as on Bordet-Gengou agar.

AUTHOR'S SUMMARY.

PROTECTIVE ACTION OF CAROTENE AGAINST INFECTION IN VITAMIN A DEFICIENCY. R. G. TURNER and E. R. LOEW, J. Infect. Dis. **52**:102, 1933.

Carotene is protective against bacterial invasion of the upper respiratory tract and the development of the pathologic systemic conditions accompanying vitamin A deficiency in rats. Carotene in olive oil has been stabilized for a period of four months or longer by the addition of hydroquinone to the solution. Both hydroquinone and quinhydrone act as inhibitors in the conversion of carotene to achrocarotene. Vanillin hastens this reaction. Solutions kept under nitrogen fade more rapidly than those in contact with air. Carotene therapy reduces the number of spontaneous suppurative lesions in the upper respiratory tract occurring in animals deprived of vitamin A; xerophthalmia is cured in 100 per cent and normal health regained in 74 per cent. The percentage incidence of bacteria in the nasal cavities and middle ear in animals fed active carotene is noticeably less than that encountered in animals given faded carotene or that in animals receiving no source of vitamin A.

AUTHORS' SUMMARY.

AGGLUTINATION EXPERIMENTS AS EVIDENCE OF THE DIVERSITY OF NONHEMOLYTIC STREPTOCOCCI. H. W. CROWE, J. Infect. Dis. **52**:192, 1933.

A method of cataloging the streptococci is briefly described. Four criteria are suggested for the determination of what should constitute different races of microbes: first, cultural and microscopic characters; second, disease-producing characters; third, special morphologic and biochemical characters, and fourth and most important for clinical medicine, serologic characters. Two of the last three must show definite differences. On the medium the formula of which is given in this article and by fermentation (criterion 3) individual streptococci show sharp differences. By agglutination tests with monovalent rabbit serums (criterion 4) it has been shown that certain streptococci, differing on chocolate agar but similar in fermentation, are heterologous in type. They are definitely distinct organisms, since two of three criteria are satisfied. By inference it may safely be assumed that the nonhemolytic streptococci are a large group containing many varieties. The differences between these varieties cannot reasonably be ascribed to mutation but are to be considered fundamental.

AUTHOR'S SUMMARY.

INVESTIGATION OF CERTAIN SYNTHETIC GLUCOSIDES FOR ANTIGENIC PROPERTIES. A. G. WEDUM, J. Infect. Dis. **52**:203, 1933.

Twenty-two glucosides of known composition were synthesized. These represented a wide range of structural formulas and solubilities and, in the condition in which they were used, a range of physical state from simple solutions through suspensoids and suspensions. The dispersing mediums were: water; saline solution; glycol; 10 per cent and 20 per cent alcohol; 0.5 per cent gelatin, and 0.5 per cent gelatin, 95 parts, plus acetone, 4 parts. These glucosides were tested for antigenic properties by injecting them into guinea-pigs for the production of precipitins, agglutinins and anaphylactins. In no instance were precipitins, agglutinins or evidence of anaphylaxis demonstrated. Pseudoprecipitation and pseudo-agglutination sometimes occurred.

AUTHOR'S SUMMARY.

EFFECTIVENESS OF STANDARD DIPHTHERIA ANTITOXIN AGAINST ALL TYPES OF DIPHTHERIA INFECTION. O. R. POVITZKY, M. EISNER and E. JACKSON, J. Infect. Dis. **52**:246, 1933.

Toxins derived from different types of Bacillus diphtheriae seem to be identical in their response to the standard diphtheria antitoxin. This is true whether the antitoxin is injected or whether it is developed in the animal body subsequent to immunization with toxoid. B. diphtheriae-gravis kills with a smaller number of organisms than B. diphtheriae-mitis and other strains. It probably produces toxin more rapidly in the human or animal body. The difference, however, is only in

degree, not in kind. The animals infected with gravis can be saved when the antitoxin is given early and in sufficient quantity. Hence it may be inferred that the present standard toxin and antitoxin are suitable for use in the prevention and cure of diphtheria occurring anywhere.

AUTHORS' SUMMARY.

ANTIBODIES IN PLACENTAL EXTRACTS. C. F. MCKHANN and F. T. CHU, J. Infect. Dis. **52**:268, 1933.

Protein material obtained from human placentas by extraction with a 2 per cent solution of sodium chloride and refined by precipitation with ammonium sulphate has been found in qualitative tests to contain substances, presumably antibodies, which neutralize diphtheria toxin, blanch scarlet fever rashes, neutralize the poliomyelitic virus and prevent measles in exposed susceptible patients.

AUTHORS' SUMMARY.

AGGLUTININS FOR PASCHEN BODIES IN EXPERIMENTAL VACCINIA. J. C. G. LEDINGHAM, J. Path. & Bact. **36**:425, 1933.

The development of agglutinins for Paschen bodies in the serum of the rabbit in response to inoculation with vaccinia virus is described. Data are presented in the form of charts.

STREPTOLYSIN. E. W. TODD, J. Path. & Bact. **36**:435, 1933.

Two different forms of streptolysin with distinctive characteristics may be prepared by cultivating hemolytic streptococci in serum broth and by omitting the serum from the culture medium. Serum streptolysin and serum-free streptolysin are equally hemolytic and equally antigenic; the antibody produced by inoculating either of the antigens into animals will neutralize serum-free streptolysin but will not neutralize serum streptolysin. In order to obtain serum streptolysin, which is resistant to neutralization by antistreptolysin, it is essential to bring the normal serum into contact with nascent streptolysin; the combining power of streptolysin which has been formed in the absence of serum is not altered by the subsequent addition of normal serum. The failure of antistreptolysin to neutralize serum streptolysin is not influenced by the time allowed for neutralization. When hemolytic streptococci are cultivated in serum broth containing a large quantity of antistreptolysin, active streptolysin is formed which does not combine with the antistreptolysin in the culture medium. The antigenic action of serum streptolysin is confined to the production of an antibody which fails to react with the antigen itself but which reacts with a closely related antigen.

AUTHOR'S SUMMARY.

THE PRODUCTION OF TOXINS BY CLOSTRIDIUM WELCHII. L. E. WALBUM and C. G. REYMANN, J. Path. & Bact. **36**:469, 1933.

As a medium for the production of Cl. welchii toxin, ordinary veal broth containing 1 per cent peptone and, for instance, 0.25 per cent dextrose (from p_H 7.6 to 7.8, in a paraffin-oil layer) is suited. The addition of fresh muscle, coagulated meat and similar substances is superfluous. Calcium carbonate ought to be admixed to neutralize the acids formed, but in order that this neutralization is sufficiently effective the distribution of the calcium carbonate must be kept up by continuous stirring during the entire growth (this method is utilized in the State Serum Institute, Copenhagen, for the production of toxin in practice). Under these experimental conditions the largest quantity of toxin was found after from ten to eleven hours of cultivation at 37 C., and after from twenty-one to twenty-four hours at 31 C.; the minimum lethal dose (injected in vivo into mice) varied between 0.015 and 0.03 cc. The addition of defibrinated horse blood or of phenanthrenchinon to broth does not cause an enhanced production of toxin, nor does cultivation in broth boiled with liver offer any advantages. Whey with peptone gives the same

result as ordinary meat broth with peptone. Under the experimental conditions described the nonspecific acute poisonous substance (Wassermann, Kojima) is not formed in measurable quantities in the substrate containing up to 0.75 per cent dextrose. With a content of 2.25 per cent dextrose, however, it is produced in considerable quantities. The specific, thermolabile toxin has also an acute killing effect in larger doses (about from three to five times the minimum lethal dose). The toxin is most stable at p_H 6. The proteolytic (albumose-splitting) enzyme has its action-optimum between p_H 7 and 8. The gelatin-melting enzyme has an action-optimum at about p_H 6, but having passed a minimum of between p_H 7 and 8, the action of this enzyme ascends again with rising alkalinity. In view of the investigations made, the theory advanced by Dernby and Walbum regarding the production of the bacterial toxins has been applied to Cl. welchii toxin. The antitoxin-binding qualities appear to maintain themselves fairly constantly during the growth of the culture, notwithstanding the fact that the curve for the direct action of the poison gradually declines rather strongly.

AUTHORS' SUMMARY.

EXPERIMENTAL TUBERCULOSIS: II. SUPERINFECTIONS. A. BOQUET, Ann. Inst. Pasteur **50**:5, 1933.

Dermal inoculation of virulent tubercle bacilli into tuberculous guinea-pigs after sensitivity to tuberculin developed resulted in a nodule the evolution of which was characterized by a shortened period of incubation. The state of hypersensitivity rapidly reached a maximum, but immunity followed more slowly. The lesions gradually appeared more quickly and became less grave, finally showing the necrotic and spontaneously curing lesions of Koch's phenomenon. The skin, membranes and subcutaneous tissues became refractory before other parts. Some inoculated areas, e. g., testicular tissue, at the time the skin was refractory showed progressive destruction by sclerosis or caseation. Refractory cutaneous tissues still allowed indirect involvement of lymph nodes. Somewhat similar results were obtained with the rabbit but these were less marked in degree. The change in resistance appeared to be concerned, among other things, with the presence of phagocytic cells and their increased lytic properties.

FROM AUTHOR'S CONCLUSIONS.

Immunology

THE ANTIBODY CONTENTS OF THE SERUM OF LEPERS. M. A. GOHAR, Zentralbl. f. Bakt. (Abt. 1) **122**:516, 1931.

Nodules from patients with nodular leprosy were excised under strict aseptic precautions, triturated with saline solution and the supernatant fluid used in testing for complement-fixing antibodies and for agglutinins in the patient's serum. Eighteen samples of serum were employed, and none showed complement fixation or agglutinins against the leprosy bacilli in the triturated emulsions. The author concludes that further work must be done to prove that the leprosy bacillus is the only organism involved in leprosy.

PAUL R. CANNON.

Tumors

GLIOMAS IN THE REGION OF THE CAUDA EQUINA. JAMES W. KERNOHAN, HENRY W. WOLTMAN and ALFRED W. ADSON, Arch. Neurol. & Psychiat. **29**:287, 1933.

Of the authors' twenty-six tumors of the region of the cauda equina, twenty-five have been studied anatomically. Of these, seven arose from the conus medullaris and eighteen from the filum terminale. In both instances the histologic structure was the same and resembled the similar gliomatous tumors of the brain or the spinal cord. The most frequent type was ependymoma (cellular and myxopapillary forms); much less common were astrocytoma (protoplasmic), astroblastoma, spongioblastoma multiforme (of Strauss and Globus) and oli-

godendroglioma. The usual clinical symptoms were pain and yellow spinal fluid (when the sciatica syndrome was bilateral). G. B. HASSIN.

SPECIFIC ANTIGENIC QUALITIES OF CANCEROUS TISSUE. E. WITEBSKY and P. PÖPLAU, Ztschr. f. Immunitätsforsch. u. exper. Therap. **76**:82, 1932.

The ability of cancerous tissues to stimulate the production of cancer-specific antibodies varies. The variations in the result of the immunization depend primarily on the antigenic potency of the injected tissue and only secondarily on the qualities of the rabbits. On the other hand, the production of group-specific antibodies depends entirely on the individuality of the animal given the injection. Group-specific antibodies can be produced in an animal only if the corresponding antigenic substance is not present in the animal's own organs. Native and boiled cancerous tissues are about equally efficient. The claim of some authors that boiling is essential is disproved. By the addition of proper amounts of lecithin to the alcoholic extracts of organs or by the diminution of the dose of the antigen nonspecific reactions with noncarcinomatous tissues could be eliminated. Alcoholic extracts of normal intestines, which are known to react with cancerous antiserums, may lose their ability to react in a nonspecific manner when properly prepared for the complement-fixation test (evaporation and resuspension in salt solution).

I. DAVIDSOHN.

CHEMICAL AND SEROLOGIC FRACTIONS OF CANCER EXTRACTS. ELISA MORELLI, Ztschr. f. Immunitätsforsch. u. exper. Therap. **76**:305, 1932.

The difficulty in the employment of alcoholic cancer extracts lies in the fact that they contain besides cancer-specific lipoids species-specific, group-specific and organ-specific lipoids and, finally, nonspecific lipoids. The group-specific lipoids can easily be removed by absorption with the proper red blood cells. The other antigenic fractions are difficult to remove and therefore are a source of serious mistakes. Lehmann-Facius recently published a method of separating the cancer-specific portion from the others by means of fractional extraction. Morelli checked the work of Lehmann-Facius, with negative results. Using the same technic, she was equally unsuccessful in trying to separate the Forssman antigenic fraction of human tissues from the group-specific fraction. I. DAVIDSOHN.

PRIMARY CANCER OF THE LUNG AFTER CHRONIC ABSCESS. P. W. SSIPOWSKY, Ztschr. f. Krebsforsch. **36**:67, 1932.

The author describes a bronchiogenic cancer originating in the thickened wall of an old abscess cavity of the lung, which he infers was due to the chronic irritation of continued and attenuated infection. For comparison he also describes a somewhat similar case in which cancer developed from a tuberculous cavity. From the general similarity, he questions the importance of tuberculous infection per se as a factor in bronchiogenic cancer, and suggests that the element actually concerned is any irritation which might cause a chronic, productive, inflammatory process.

H. E. EGGERS.

COMBINED PULMONARY TUBERCULOSIS AND CARCINOMA. S. DERISCHANOFF, Ztschr. f. Krebsforsch. **36**:82, 1932.

Of ninety cases of pulmonary carcinoma observed at the North Caucasian University clinic during the years from 1923 to 1930, 16.75 per cent were associated with active tuberculosis. The lesions pursued independent courses, without evidence of any mutually restrictive effects. Tubercle bacilli could rarely be found in the sputum, since apparently the cancer shut off access of the organisms to it. Apparently old chronic tuberculosis predisposes to cancer by chronic irritation, whereupon the cancer so lowers the local resistance as to permit the infection again to become active. Ordinarily both types of involvement were found in the

same lung, with an absence of both in the other. Combined metastasis to distant organs was observed with some frequency. The cancer tissue may be destroyed, like normal tissues, by the infection, and may show tubercles of both the exudative and the productive type.

H. E. Eggers.

Experimental Carcinoma of the Gallbladder. L. I. Genkin and J. D. Dmitruk, Ztschr. f. Krebsforsch. **36**:104, 1932.

The authors have attempted unsuccessfully to reproduce the experimental results reported by Kazama and by Leitch, in the production of cancer of the gallbladder by the introduction of calculi or other foreign bodies. Unlike the writers cited, who used guinea-pigs, Genkin and Dmitruk performed their experiments on rabbits, and although four years were allowed in the case of some of their animals, the only changes found, with two exceptions, were those of chronic inflammation. In the two that showed changes beyond this, the changes were of papillomatous or adenomatous character. As regards the priority of concretions or of cancer in this organ, the authors point out that proliferative changes may occur without the presence of stone, which is then likely to form as a result of stasis, infection or some other process. That cholecystitis is an important factor in the causation of cancer of the gallbladder they do not dispute, but they believe that the undue frequency of calculi in association with cancer is due to their frequent association with cholecystitis, while in some cases the stones may appear secondary to the malignant process.

H. E. Eggers.

Diagnostic Value of Diastase-Activating Substances in the Urine in Cancer. P. Gereb, Ztschr. f. Krebsforsch. **36**:115, 1932.

A diastase-activating substance has been reported in the urine of patients with cancer, which, while occurring in other diseases, does so less frequently than in malignant disease. Gereb studied this phenomenon with a view toward establishing its diagnostic applicability. He found that while the substance was present in the urine of 69 per cent of his patients with cancer, it was present also in that of 23 per cent of almost a thousand noncancerous controls, so that in his opinion, while it may have some indicative value, it can by no means be considered as the basis of a specific reaction.

H. E. Eggers.

Attempted Production of Rat Sarcoma by Tomato Juice. W. A. Collier and R. Jaffe, Ztschr. f. Krebsforsch. **36**:126, 1932.

The success in the induction of peritoneal sarcomatosis of the rat by repeated injections of unsterile tomato juice, or of organisms obtained from it, as reported previously by Bellows and Askanazy, was not obtained by these writers. The only changes observed in rats and mice after this treatment consisted in the appearance of inflammatory lesions. In an appended note, Askanazy states that after his and Bellows' initial success attempts at reproduction of the positive results have been unsuccessful.

H. E. Eggers.

Rarity of Cancer in Egypt and Its Probable Cause. P. Schrumpf-Pierron, Ztschr. f. Krebsforsch. **36**:145, 1932.

The author previously reported on the incidence of cancer in Egypt, and found that it is only about one-tenth as frequent there as in Europe or America, even despite the occurrence there of cancer caused by Bilharzia, which constituted 13 per cent of the total cases of malignant conditions. Gastro-intestinal cancers are especially rare, this holding true even of Europeans living there. In his explanation of this disparity, the author expresses the belief that climatic and racial factors may be excluded, and he thinks that it is purely a matter of nutrition. The soil of Egypt has an unusually high content of magnesium salts, and it is

the resultant high intake of these, with a lessened ingestion of potassium salts, which he believes is responsible for the difference in the incidence of cancer.

H. E. Eggers.

Diet and Cancer. S. Peller, Ztschr. f. Krebsforsch. **36**:217, 1932.

With reference to the belief that the alleged increase in cancer may be a matter of changed dietary, particularly of the increase in the consumption of meat that has been conspicuous in modern times, Peller summarizes the evidence against this view. If it were true, cancer should be outstandingly a disease of the more favored social classes, which is directly contrary to fact as demonstrated particularly in British mortality statistics, which show that the disease is commonest in the class of unskilled laborers and least frequent in the so-called upper class. It is true that cancer of the lower part of the gastro-intestinal tract is commoner in the latter class, but this would appear to be primarily a matter of the lower incidence in it of cancers higher up. While Peller recognizes alcoholic indulgence as a factor in the incidence of cancer, he finds that when this is combined with a high intake of meat, as in the landlord class, there is less cancer than among hired employees, such as waiters, in whom a high ingestion of alcohol is combined with irregular hours and sexual irregularity. It is in connection with cancer of the upper part of the alimentary tract that alcohol would appear to be most important. Finally, Peller doubts greatly that the increase of cancer as shown by mortality statistics is actual; he believes that it can be accounted for by altered age distribution and increased diagnostic accuracy, and that if there is a change, it is in the line of lowered incidence if these elements are considered.

H. E. Eggers.

A Local Study of the Incidence of Cancer. L. Endrös, Ztschr. f. Krebsforsch. **37**:165, 1932.

The district of Zusmarshausen, in Swabia, offers unusual features which make it particularly suited for a local study of the incidence of cancer. The population has remained essentially unchanged in character during the last eighty years; there has been no industrialization with the associated economic upheavals; the region is one of very high mortality from cancer; the only change in habits is one of some interest in this connection—a rather radical improvement in the dietary, which originally was almost wholly vegetable and monotonous, with a deficiency of fat and protein and an excess of carbohydrate. It is now better balanced though still largely vegetarian. During the eighty years considered there has been no appreciable change in the mortality from cancer, though shorter periods show variable fluctuations. No relation of the incidence to the diet could be detected, nor was there any relation to the character of the potable water. This is true, too, of the character of the subsoil, but there did appear to be a relationship to the terrain in that localities near bodies of water showed a relatively high incidence.

H. E. Eggers.

Inheritance in Cancer. J. Cholewa, Ztschr. f. Krebsforsch. **37**:215, 1932.

Cholewa presents, along with a summary of the literature, several instances of apparent familial cancer. One of these concerns a mother with bilateral mammary cancer and a cancer of the uterus, who had two cancer-free sons and ten daughters, five of whom died of cancer, of the uterus or ovary and the breast. In the third generation there already have been three cases of cancer, of the uterus, breast and rectum (male). In the second family, both parents and four of eight offsprings have died of cancer, of the uterus in the female patients, and of the stomach in the male patients. In the third family, the great-grandfather died of carcinoma of the stomach. There were no cases of cancer among his ten children, but the next generation showed seven cases among eight persons, and so far there have been two in the last generation. The fourth case, which

he cites from unpublished data obtained from Professor Miculicich, concerns the apparent familial incidence of a neoplastic diathesis of mesenchymal tissue. Of three sisters, one had a uterine fibromyoma, one leukemia and one a uterine sarcoma.

H. E. Eggers.

Technical

Two Useful Staining Methods for the Human Hypophysis. F. B. Kindell, Bull. Johns Hopkins Hosp. **53**:56, 1933.

The hypophysis is fixed for twenty-four hours in Zenker's fluid to which a dilute solution of formaldehyde has been added, or, more correctly, 90 cc. of Zenker's fluid without acetic acid plus 10 cc. of a 40 per cent solution of formaldehyde, the mixture being made immediately before use. The hypophysis should be cut into two or, better, into three blocks. Paraffin sections are made; these are treated to remove the paraffin and are then passed through graded alcohols; the mercury precipitate is removed in the usual way.

Fuchsin-Methyl Blue Method.—1. Wash in water.

2. Immerse for from fifteen seconds to two minutes, or longer, in a freshly prepared 1 per cent solution of potassium permanganate.

3. Wash in water.

4. Immerse for the same length of time as in 2 in a 5 per cent aqueous solution of oxalic acid.

5. Wash well, and follow by washing in distilled water.

6. Stain with a 5 per cent solution of aniline acid fuchsin at 60 C. Heat the stain gently on the slide until it steams, not boils, and allow to cool for from six to ten minutes. The dye can be poured back into the bottle and used again. In the preparation of this solution, Altmann's aniline fuchsin, not more than from 5 to 7 Gm. of fuchsin, will dissolve in 100 cc. of aniline water. The 20 Gm. of the usual formula is a waste of dye.

7. Wash in distilled water. If the section is too red, it may be decolorized somewhat by dipping once or twice in a 95 per cent solution of alcohol.

8. Immerse for from five to ten minutes in a 0.05 per cent aqueous solution of methyl blue (not methylthionine chloride, U. S. P.) until the basophil cells can be distinctly seen.

9. Differentiate quickly in absolute alcohol; clear and mount.

The eosinophil granules stain bright red; the basophil, deep blue.

Eosin-Methyl Blue Method.—Fix the tissues in Helly's fluid (a modification of Zenker's fluid). Zenker's fluid, solution of formaldehyde or Bouin's fluid may be used.

1. Wash in water.

2. Stain for from two to twelve hours in Mann's stain (1 per cent aqueous solution of eosin [water soluble, yellowish], 35 cc.; 1 per cent aqueous solution of methyl blue, 35 cc.; water, 100 cc.).

3. Wash in water.

4. Differentiate in a 95 per cent solution of alcohol containing 2 drops of concentrated ammonia water to 50 cc. of alcohol.

5. Wash in several changes of a 95 per cent solution of alcohol to remove the alkali.

6. Immerse for from thirty seconds to one minute in water acidified with a few drops of glacial acetic acid.

7. Wash in water, dehydrate quickly in alcohols, clear in xylene and mount.

The eosinophil granules stain red; the basophil, blue. The chromophobe cells and connective tissue are faint blue or almost colorless. The methyl blue in this method is an excellent nuclear stain.

Society Transactions

PATHOLOGICAL SOCIETY OF PHILADELPHIA

Regular Meeting, Oct. 12, 1933

V. H. Moon, *Presiding*

Experimental Syphilis of Mice, Rats and Guinea-Pigs. John A. Kolmer and Clara C. Kast.

Mice, rats and guinea-pigs are susceptible to infection with Spirochaeta pallida. Local lesions at the site of inoculation are rarely produced. In these animals the infection remains latent over long periods, especially in the inguinal lymphatic glands and in the spleen. In mice the brain is also quite susceptible to invasion with Spirochaeta pallida, and the infection may remain latent in this organ over long periods. In view of the extreme latency and limited distribution of syphilitic infection in these animals, it seems that serologic tests for syphilitic infection are of no value.

Experimental Air Embolism. Joseph Wolfe and Harold F. Robertson.

The amount of air necessary to produce death, when injected intravenously, differs with each animal and seems to be directly proportional to the size of the pulmonary artery and its branches. The lethal dose for a rabbit is approximately 0.5 cc. per kilogram, while for a dog it is 15 cc. per kilogram. For man it has been calculated that an amount of from 1,200 to 1,500 cc., or equal to man's vital capacity, may cause death. The speed of injection was of little importance so long as the period of injection was shorter than the time required for absorption. The injected air is found in the pulmonary artery and its branches. If the air is given in large amounts it may be found in the right ventricle, in the right auricle and even in the superior and inferior vena cava. In this manner the pulmonary circulation is partly or completely blocked. No air could be found in any of the other organs after sectioning them under water. At no time could we find that air, owing to gravity, will go against the blood stream and remain in the uppermost vessels if the animal is held in the upright position. From these experiments it appears that intravenous injection of a large volume of air may be expected to cause shock, dyspnea, cyanosis, slow pulse and convulsions. In cases in which a large volume of air is accidentally injected, it would be logical to aspirate the right ventricle since it is easily accessible. The amount of air which may be accidentally introduced during an ordinary intravenous injection is of no clinical significance.

Experiments on Chemotropism of Leukocytes. William B. Wartman, Morton McCutcheon and Harold M. Dixon.

In studying the phenomena of inflammation it is often difficult to decide whether a given effect is due immediately to bacteria and their products, or whether destroyed body cells and tissues have been contributory. Such a question arises in regard to attraction of leukocytes in inflammatory areas. Experiments were made in vitro to determine whether dead body cells (dried leukocytes) are able to attract live leukocytes. A clump of dried cells and a drop of fresh blood from the same person were spread between a slide and coverslip. Under the microscope the number of leukocytes making contact with the attracting body within an hour was counted and compared with the number which, distant from the attracting

body and wandering at random, made contact with an imaginary attracting body of the same size as the real one. The numbers obtained were on the average 10 and 2 per hour, respectively. Paraffin and bits of glass sometimes attracted and sometimes did not attract cells. A number of different micro-organisms attracted leukocytes vigorously. With Staphylococcus albus, an average of 21 leukocytes per hour made contact with the attracting body, showing that under the conditions of these experiments micro-organisms attract leukocytes more vigorously than dead body cells do.

Regular Meeting, Nov. 9, 1933

V. H. Moon, *Presiding*

Peculiar Nephritis Associated with Acquired Syphilis: Report of a Case. John T. Bauer.

A colored man, aged 41, who stated that he had acquired syphilis sixteen years before and received little treatment, was admitted to the Pennsylvania Hospital with symptoms of chronic nephritis and hypertension. Hematuria and oliguria were never noted. His urine contained a moderate amount of albumin and moderate numbers of hyaline casts, leukocytes and undescribed crystals. The blood urea nitrogen rose rapidly over a period of six weeks from 69.5 to 180 mg. per hundred cubic centimeters, and the blood creatinine, from 7.2 to 13.4 mg. per hundred cubic centimeters. His reactions to a Wassermann test of the blood and to the Kahn test were strongly positive. Death resulted from uremia and terminal pneumonia.

The interesting changes post mortem were seen in the aorta and kidneys. An unsuspected saccular aneurysm was found in the ascending portion of the former, and in the latter extensive inflammatory changes unlike those usually seen in chronic nephritis were observed. The convoluted tubules were greatly dilated and contained granular débris and crystals of cholesterol. An interstitial infiltration of round cells existed chiefly about the tubules, occasionally in focal collections which bulged into the tubules but nowhere were those cells seen to break through the tubular epithelium. The collecting tubules contained a few hyaline casts. Although some of the glomeruli showed evidence of vascular change, they were not involved in the inflammatory process. Vascular changes were confined to the larger renal vessels, and little change was seen in the arterioles. No spirochetes were found.

From the descriptions and evidence presented by Rich (*Bull. Johns Hopkins Hosp.* **50**:357, 1932), it was thought that the renal lesion represented syphilitic nephritis.

Paradoxical Embolism: Report of a Case. James Taylor.

A white woman, aged 45, was admitted to the Pennsylvania Hospital three weeks after a sudden onset of illness which began with chills, cough, blood-streaked sputum, sweating, pain in the epigastrium and weakness. She grew worse gradually, and on admission to the hospital the signs were suggestive of a resolving bronchopneumonia. A few hours after admission cyanosis accompanied by tachycardia, an extreme drop in blood pressure, sweating and delirium developed. The temperature began to rise, and a marked precordial activity was noted. Shortly afterward she died.

Necropsy revealed thrombi filling the left femoral and right internal iliac veins. Emboli were present in the small branches of the pulmonary and left renal arteries and in the splenic artery. Infarcts of some duration were seen in the lungs, left kidney and spleen. A long twisted embolus filled a patent foramen ovale and appeared to be on its way through the orifice. Massive pulmonary embolism was the immediate cause of death.

CORONARY OCCLUSION WITH ANEURYSM OF VENTRICLE: REPORT OF A CASE. ALLAN D. WALLIS.

A case of aneurysm of the left ventricle is reported. A white man, aged 42, had suffered from dyspnea and dependent edema for two years following an acute attack of pain in the upper left side of the chest. Because of a transient loss of consciousness he was admitted to the hospital, where he remained in a state of advanced decompensation for six weeks until his death. Autopsy showed a recanalized occlusion of the left circumflex coronary branch with a large saccular aneurysm of the posterior wall of the left ventricle. The aorta showed marked arteriosclerosis without evidence of syphilis.

INTERAURICULAR SEPTAL DEFECT ASSOCIATED WITH MITRAL STENOSIS. W. GRADY MITCHELL and JOHN T. BAUER.

A white man, aged 40, suffered for six years with dyspnea, cough, hemoptysis, precordial pain and terminal cyanosis. The cardiac findings were: (*a*) enlargement, especially of the left side along the left auricle and pulmonary conus, when the heart was seen by fluoroscopy; (*b*) a dense shadow moving from side to side in a slightly oval orbit in the region of the mitral valve observed on fluoroscopy; (*c*) electrocardiographic tracings showing partial auriculoventricular block; (*d*) an accentuated pulmonary second sound and a doubtful diastolic murmur at the base, and (*e*) a poorly defined systolic murmur over the pulmonic area.

At necropsy the heart was found to be huge, weighing 620 Gm. The right ventricle and auricle were greatly hypertrophied and somewhat dilated. The foramen ovale was closed, but an ostium primum remained beneath it. No ventricular septal defect existed. The tricuspid and mitral rings were formed. The tricuspid valves were well formed except for a wide zone of separation between the anterior and medial cusps. The mitral valve was fixed, firm and obviously stenotic. The cusp opposite the ostium primum showed marked calcification which extended from the ring into the myocardium and beneath the endocardium of the left ventricle and into the valve for a short distance. The chorda tendineae were thickened and shortened. Several atypical chords, present on the ventricular aspect of the mitral valve, were suggestive of Chiari's network. The area of calcification was associated with the formation of bone. The aortic valve and ring were much smaller than the pulmonic.

PERIARTERITIS NODOSA: REPORT OF A CASE. DAVID L. FARLEY and JAMES S. TAYLOR.

A white woman, aged 35, was admitted to the service of Dr. Hollingshead, Cooper Hospital, Camden, N. J., on Oct. 3, 1932. Except for bronchial asthma for nine years she had always enjoyed good health. Her complaints were pain, numbness and swelling of both feet with prostration. She was found to have an eosinophilia of 72 per cent. Trichinosis was suspected, and a biopsy was made on muscle. This revealed the lesions of periarteritis nodosa. She died two and a half months later. Necropsy revealed generalized periarteritis nodosa.

OCCURRENCE OF COINCIDENT CALCULUS AND TUBERCULOSIS OF THE KIDNEY. CHARLES R. TATNALL.

The occurrence of calculus in cases of renal tuberculosis is uncommon; the total number of such cases available is eighty-two, two of these from the Pennsylvania Hospital being reported for the first time. The incidence of calculus in tuberculous kidneys is variously placed at from 1 to 2.7 per cent. Tabulation of the cases shows them to occur mainly in patients in middle life without preference for either sex. It has been demonstrated that the tuberculosis may be the cause of the formation of a calculus, and it has been suggested that the irritation from the presence of calculi may predispose to tuberculous infection, but in most cases the coexistence of tuberculosis and calculus seems to be accidental.

(Complete reports of these cases will be published in the Ayer Clinical Laboratory Bulletin no. 13.)

Book Reviews

Diseases of the Heart Described for Practitioners and Students. By Sir Thomas Lewis, C.B.E., F.R.S., M.D., D.Sc., LL.D., F.R.C.P., Hon.D.Sc. (Michigan), Physician in Charge of Department of Clinical Research, University College Hospital, London; Physician of the Staff of the Medical Research Council; Physician in Chief (Pro Tem.), Peter Bent Brigham Hospital, Boston; Honorary Fellow, New York Academy of Medicine; Corresponding Member, Association of American Physicians and Interstate Postgraduate Medical Association. Price, $3.50. Pp. 297, with 45 figures. New York: The Macmillan Company, 1933.

It is a good thing to have a book written by a competent author who is impelled to write because he has a message and who has a definite objective and a definite plan. In carrying out his purpose of writing not a book of reference but one that will help the practitioner to recognize and treat the more common diseases of the heart, Sir Thomas boldly breaks with tradition, discards old classifications and omits all that does not directly fit into his plan. He stresses not the laboratory but the bedside, not what others think but what he knows by experience, not anatomy but function, not theories but facts. When it is added that Sir Thomas has written in an orderly manner, with his usual clarity and conciseness and with the zeal of a missionary inspired to preach a new gospel, one may understand that the work is sui generis, one that is bound to attract wide attention and to elicit both extravagant praise and vehement criticism. In fact, the reviewer has already heard one competent physician declare it "the best volume on heart disease ever written," and another equally competent call it "rotten."

These diverging views can be understood. There are chapters that for their purpose are models. Those on angina pectoris and coronary thrombosis are word pictures with the clear lines of a steel engraving. The chapters on tachycardia, effort syndrome, rheumatic carditis, arteriosclerosis, syphilis of the heart and hypertension are most excellent. Lewis is not bound by tradition as to diagnosis, prognosis or treatment. If his experience shows him that percussion is of less value than palpation or roentgenograms in determining the size of the heart, he says so frankly. He freely admits that there are many gaps in the knowledge. He is strong in common sense. In no place is this common sense more in evidence than in his detailed outline of treatment, not only of the disease, but of the patient. And it is refreshing to hear his note of optimism as to many forms of heart disease.

The very plan of the work, with its commendable aim at simplicity, lays it open to criticism on the score of sins of omission. No two would agree as to what symptoms and signs, what drugs and what etiologic and pathologic features should be omitted. Thus the reviewer believes that his differential diagnostic paragraphs are among the most faulty in the book; others might not agree with this view. Such criticisms are inevitable, nor would they be avoided were Lewis himself or any one else to rewrite his book.

Some sins of commission are not so excusable. The author, usually dogmatic and announcing *ex cathedra* opinions without argument, at times adopts the attitude of an advocate to support some view to which he is partial. Shall this be called a defense reaction? He is belligerent and peppery when he discusses such questions as mitral regurgitation or the mechanical theory of heart failure. "Failure of compensation" is as the red rag to the bull. And in these arguments and invectives he is not always quite fair in stating the views of others. Nor is his position, as the reviewer sees it, always sound. He is not justified in ignoring—he practically does this—mitral regurgitation, and stressing alone stenosis, its murmurs and its effect on health. And why should he, as he virtually does, contend that because

with stenosis or coarctation of the aorta the heart does not give out early, the degree of obstruction is really of little moment? Nor is he alone in regarding the heart muscle and cardiac reserve as of prime importance; Martius, Krehl and others long ago wrote much on this topic.

The reviewer agrees with him as to the importance of the use by the practitioner of the unaided senses in reaching a diagnosis. But if the physician follows his advice—this is the tenor of the work—and uses the x-rays, electrocardiograph and sphygmomanometer only exceptionally, both the physician and the patient will often be deprived of useful knowledge to which they are entitled.

Moreover, there is an attitude of mind on the part of Sir Thomas that seems remarkable in one whose research work has taught him the value of accuracy and the worth of details. To take the position regarding the physician that he is to be content merely with essentials, that there are signs of disease which are interesting but he need not know them. that to judge of blood pressure by the unaided finger is good enough for him, and that after he graduates he will, of course, have nothing to do with the laboratory is not flattering to the practitioner; it relegates him to the ranks of mediocrity and classes him as nonprogressive. Fortunately all practitioners will not be satisfied to keep away from the laboratory and its methods, nor unthinkingly to accept opinions as correct merely because they are delivered by one so competent to give them as Sir Thomas Lewis. Many, most of those recently graduated, are well educated students, independent workers and thinkers. Sir Thomas is writing too much down to the level of the poorer practitioners—alas, there are many such. But is this attitude of the author the best one from the standpoint either of imparting information or of stimulating the reader to seek further?

One could go on praising and condemning his book. One could question whether undue emphasis has been laid on signs of heart failure outside the heart, on whether angina and congestion are really the only important features to be considered by the physician. Enough has been said to show that a work on a new model has been put forth, a work that is provocative, one that has merits that will be copied by later writers on cardiology as well as on other subjects, and one that has faults that should be avoided. It may interest the readers of a journal of pathology to know that this book, essentially clinical, contains an astonishingly small amount of pathology. What little there is, however, has been admirably selected, is sound and has an immediate value in explaining symptoms and disturbances of function. There is almost no consideration of microscopic pathology.

The format of the book is attractive. Several errors in typography and in the use of English can be corrected in later editions, which will surely be demanded.

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